COLLECTED STUDIES
ON THE
PATHOLOGY OF WAR GAS POISONING

PUBLISHED ON THE FOUNDATION
ESTABLISHED IN MEMORY OF
ANTHONY N. BRADY

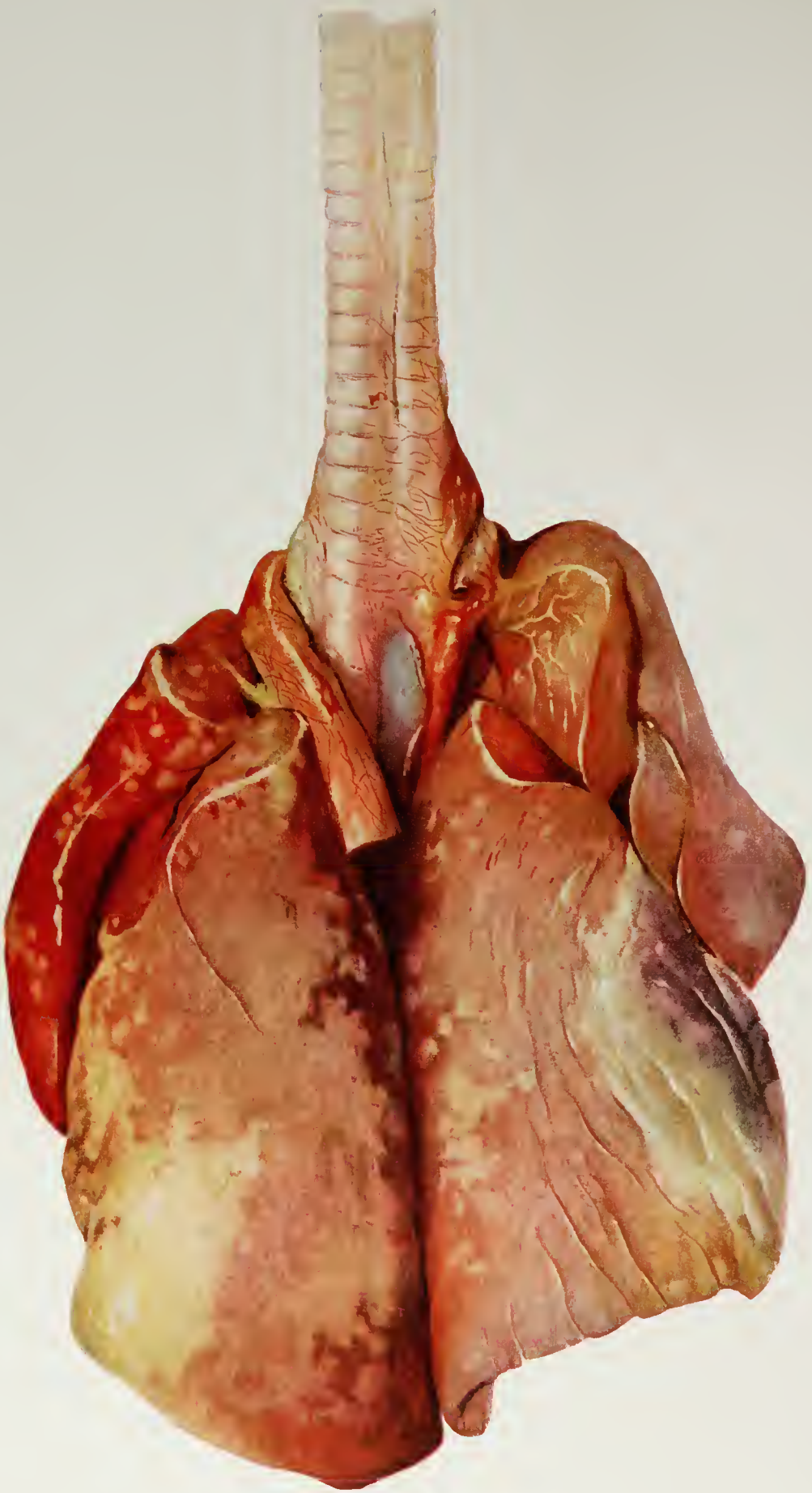

PLATE I

BRONCHO-PNEUMONIA AND FIBRINO-PURULENT PLEURISY IN THE DOG 8 DAYS AFTER GASSING WITH CHLORINE.

COLLECTED STUDIES ON THE

PATHOLOGY OF WAR GAS POISONING

FROM THE
DEPARTMENT OF PATHOLOGY AND BACTERIOLOGY
MEDICAL SCIENCE SECTION
CHEMICAL WARFARE SERVICE

UNDER THE DIRECTION OF
M. C. WINTERNITZ, MAJOR, M.C., U.S.A.

PUBLISHED WITH THE CONSENT OF
THE SURGEON GENERAL, U. S. ARMY, AND
THE DIRECTOR, CHEMICAL WARFARE SERVICE

NEW HAVEN
YALE UNIVERSITY PRESS
LONDON·HUMPHREY MILFORD·OXFORD UNIVERSITY PRESS
MDCCCCXX

THE ANTHONY N. BRADY MEMORIAL FOUNDATION

The present volume is the first work published by the Yale University Press on the Anthony N. Brady Memorial Foundation, which was established June 15, 1914, by members of the family of the late Anthony N. Brady to enable the University to declare operative the agreement for an alliance between the New Haven Hospital and the Yale School of Medicine. In addition to the pledge of endowment for this purpose the donors erected for the University on the grounds of the Hospital a clinical and pathological laboratory, and have since, through additional gifts to supplement the income of the Memorial Foundation, made possible the publication of this and other works by members of the Faculty of the School of Medicine at Yale.

FOREWORD

When the United States entered the world conflict, her scientists laid aside academic pursuits and seized upon such national problems as fell within their sphere.

The introduction of poisonous gases among the weapons of war had so modified the character of hostilities as to call for a revision of offensive and defensive measures. With the Bureau of Mines was a group of scientists who, being familiar with the control of toxic mine gases, were called upon by the director, Van H. Manning, when he formulated the nucleus of what grew under his guidance out of all proportion to the original plan and, in July, 1918, became an independent department of the army—The Chemical Warfare Service.

In such a scheme medicine of necessity occupied an important place. Professor Yandell Henderson of Yale, who had previously contributed materially to the physiology of the mine gas work was, therefore, chosen by Director Manning to organize a medical science section. As there was no definitely designated place for the localization of the work at its inception, Henderson naturally availed himself of the facilities offered by Yale University, and in June, 1917, the Medical Science Section was established in New Haven with the creation of a field station.

Every effort was made to conduct the work with such attention to precise quantitative methods as would assure its high scientific status. Three lines of work were begun—physiology and toxicology, intermediary metabolism, and pathology under the direction of Professors Henderson, Underhill, and Winternitz respectively.

By the autumn of the same year definite results had been obtained. In the toxicological work Marshall and Barbour had perfected the closed chamber method for the exposure of experimental animals to known concentrations of gas, and preliminary results had been obtained by them concerning the lethal concentration of several gases on different species.

Underhill had collected data in his specific field, the most important being the observation that the mortality was unusually low among animals which had been bled in the course of his experiments. The investigation and elaboration of this discovery by Underhill and his co-workers have led to the most important contribution of the Medical Science Section; namely, a method for reducing the mortality from pulmonary irritant gases in the acute or edema stage.

In pathology the work was confined to a study of gross lesions in animals which had been utilized for the experiments quoted. Progress had been retarded by the lack of necessary assistance and equipment pending the completion of the Brady Laboratory of Pathology.

At this juncture the grounds and partially completed buildings of the proposed American University at Washington, D. C., were secured by the Bureau of Mines to carry on many phases of the work of the Division of Chemical Research under G. A. Burrell, which

had developed apace with the medical research. Partly with a view to centralization and partly because the presence of the Chemistry Section at this station would assure an ample supply of the various gases under test, it seemed advisable to establish there a toxicological section, primarily to assay the action of these gases upon animals. Work of this nature was, therefore, transferred from New Haven with Marshall, who was then placed in charge of the new Department of Pharmacology and Toxicology at Washington.

To trace the growth of each of the several branches beyond this point is beyond the scope of this record, wherein the work in pathology alone is to be presented.

With animal experimentation at the American University, anatomical investigations became imperative, but while material facilities for the work were obtained, no satisfactory progress was forthcoming in view of the dearth of available trained pathologists. That this difficulty was eventually overcome, however, is sufficiently evidenced by the contributions to this monograph which have emanated from the laboratory in question.

The laboratories of pathology at New Haven and Washington have maintained the closest co-operation, and by occasional interchanges in personnel, the work of each has been materially advanced.

At the Brady Laboratory in New Haven, where the work was carried on prior to the completion of the new Yale Chemical Warfare Service Laboratory for Medical Research,* activities were governed largely by the character of material which was supplied in abundance by Underhill and his associates, and in this way each animal was made to serve a dual purpose. The fact that few gases were studied has been amply compensated for by the many subjects used, since with these it has been possible to investigate progressive lesions from those almost immediately after gassing, through the various acute periods to the residual chronic changes, which are in turn associated with more remote complications.

The observation that chronic lesions may persist after the acute effects of gas poisoning have disappeared, is not known to have been emphasized previously, and constitutes one of the most important contributions from the New Haven Laboratory. An explanation for the persistence of symptoms in man is thus offered, and the knowledge should be a guide in the prophylaxis against exacerbation of symptoms which might result from such chronic pulmonary conditions.

At the same station the importance of bacteria in lesions of the respiratory tract was indicated. The inhibitory effect of gas upon the protective mechanism of the upper respiratory tract is now known to be followed by an invasion of bacteria into the finer ramifications of the bronchial tree. In all probability this discovery has a wider application, for by emphasizing the portal of entry in other conditions where the protective function of the upper respiratory tract is impaired, it may suggest means of prophylaxis against pneumonia.

The papers included in this monograph have been made possible only by the hearty co-operation of the entire personnel of the two laboratories indicated in the subjoined chart. This opportunity is taken to thank the members of the institutions indicated below for their interest and co-operation, which have materially facilitated the work and have greatly increased whatever value it may have.

* The new home provided by Yale University for the Chemical Warfare Service is a large brick building occupying the northeast corner of Park and Oak Streets in New Haven. It is to house the various branches of the service in that city, and will obviate difficulties of communication besides providing ample facilities to replace the much overtaxed hospitalities which have been extended to the work by other laboratories of Yale University. It is hoped that complete co-operation may be established in the new environment.

To the Corporation of Yale University for its kindness in permitting me to undertake the direction of this work, as well as for its generosity in placing its laboratory facilities at my disposal;

To the Director of the Bureau of Mines, Van H. Manning, to his assistant in charge of the war gas investigations, G. A. Burrell, and to Professor Yandell Henderson, in charge of the Medical Science Section, for their support of the Department of Pathology and Bacteriology;

To Colonel Burrell, and to his assistants, Lieutenant-Colonel Bancroft and Major West of the Publication Department of the Chemical Warfare Service, American University, for their continued support in the production and publication of the monograph;

To Colonel F. F. Russell, in charge of the Division of Laboratories and Infectious Diseases in the Surgeon General's office, U. S. A., for the army personnel detailed to aid in these studies;

To Colonel W. O. Owen, in charge of the Army Medical Museum, for the valuable services of trained artists from his staff;

To Major General Sibert and to Colonel W. C. Lyster of the Chemical Warfare Service, for their continued support of the investigations and for their aid in making the publication of this work possible.

M. C. WINTERNITZ.

October 1, 1918.

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Chemical Warfare Service, U. S. A.—Major-General W. L. Sibert.
Research Division—
Medical Science Section—Col. W. J. Lyster.
Pathology and Bacteriology—Major M. C. Winternitz, M.C.

NEW HAVEN STATION

1. PATHOLOGY—Capt. Robert A. Lambert, M.C., in charge; Contract Surgeon Leila Jackson, Ass't in charge.
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   b. Histological Technique—Leon S. Stone, civilian; Pvts. Joseph Mardiros, C.W.S., Burech Rachlis, C.W.S.
   c. Autopsy Technique—Sgt. Myron S. Jared, C.W.S.; Pvt. Vincent A. Caso, C.W.S.

2. BACTERIOLOGY—George H. Smith, Ph.D., in charge; Pvts. Earl R. McCarthy, C.W.S., Carleton T. Smith, C.W.S., Charles W. Russell, C.W.S., Sears P. Doolittle, C.W.S., Earl Southworth, C.W.S.

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* Detailed by Col. W. O. Owen, Army Medical Museum.

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THE PATHOLOGY OF CHLORINE POISONING

BY

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THE PATHOLOGY OF CHLORINE POISONING

INTRODUCTION

The asphyxiating properties of chlorine in the gaseous state have been recognized from very early times, and in the literature dealing with industrial accidents are found a number of references to instances of temporary disablement or death from accidental exposure to this gas in factories where the gas was being generated.

It was not, however, until the second year of the present war, when the Germans introduced gas as a fighting weapon, that the noxious character of chlorine received any particular attention.

In this new rôle, chlorine was first employed at Ypres on April 15, 1915, when great quantities of the gas were released forming clouds, which were blown across a sector of the allied lines held by the French and Canadians. Numerous casualties resulted, a high percentage of the exposed troops being disabled, with many deaths. Since that time this modern method of chemical warfare has come to occupy a more and more important place in both offensive and defensive fighting, and a number of noxious gases, in addition to chlorine, have been utilized.

Gas clouds, composed entirely or in large part of chlorine, which were used so effectively in the first months of gas warfare, are now rarely employed owing to the fact that protection against this form of attack is relatively easy. Great quantities of chlorine gas are, however, still utilized along with other gases in the preparation of gas shells, many thousands of which are consumed daily in the fighting at the present time.

The effects of chlorine gas on man as seen in the victims of gas attacks have been observed by medical officers at the front and in the base hospitals and a number of papers dealing with the symptomatology and therapy of the condition have been published. Among these may be mentioned reports by Elliott, Black and Glenny, Bibblethwaite, Lewis, Mandle and Gibson, Cumston, Williams, and Miller.

There have appeared also a few papers presenting the results of experimental studies upon animals gassed with chlorine. These by the following authors are accessible:—Schaefer, Hill, Edkins and Tweedy, Bayliss, Belancioni, Klotz, and Hunt and Schultz. The more important of the experimental studies have been carried out under the direction or patronage of the Allied Governments, and many of the reports are not yet available in published form. These have had as their object, firstly, the demonstration of the exact manner in which chlorine gas produces its harmful effects, and, secondly, the working out on this basis of a rational method of treatment. Papers dealing with the pathological anatomy and histology of chlorine gassing in man are surprisingly few in number and very disappointing in the matter of detailed description. They are limited as a rule to a discussion of the acute lesions with slight reference to the changes found in chronic cases. The criticism as

to lack of detail applies also to the reports upon the pathology of experimental chlorine poisoning, although in some of these, particularly that of Edkins and Tweedy, the acute changes in the respiratory tract are very thoroughly discussed.

MATERIAL FORMING BASIS OF REPORT

The present report deals primarily with the pathology of poisoning by chlorine gas as seen in experimentally gassed animals, with a discussion of the significance of the lesions found. The report is based on post-mortem findings in a large number of dogs utilized in experiments carried out by Dr. F. P. Underhill and his co-workers in the Sheffield Laboratory of Physiological Chemistry of Yale University for the purpose of determining the toxicity of chlorine in varying concentrations and for working out a satisfactory method of treating the condition produced. All dogs dying in the course of these experiments were transferred immediately after death to the Brady Laboratory for autopsy. Animals which did not succumb within a few days after gassing were taken to a farm, where in the course of a few months a considerable number died. The majority of these chronic dogs, or "survivors," as they may be termed, were killed at intervals up to 193 days after gassing. The quantity of pathological material thus placed at our disposal amounted to 326 dogs, a much larger series than that forming the basis of any previous report on this subject. We have been especially fortunate in being able to follow a large number of these recovered or chronic animals for very long periods after gassing and thus see the more remote effects of the gas injury.

AUTOPSY FINDINGS

As might be expected, the pathological changes found at autopsy after fatal exposure to chlorine gas, vary greatly with the length of time the animal lives after gassing. For example, in a dog dying within 12 hours the lungs differ very strikingly, both grossly and microscopically, from those of a dog surviving 12 days; although it is possible after the study of a large series of animals representing all the intervening stages to make out perfectly the sequence of changes from the most acute to the very chronic lesions. In order to bring out most clearly this chain of events, it has been deemed advisable in the presentation of our data to group the animals according to the time of survival. Such a classification must necessarily be somewhat arbitrary both as regards the number of divisions made as well as the points of division between the groups. After a thorough study of all the cases we have made the following groups:

Group I. *Animals dying in the first 24 hours after gassing, "acute death."* (Number autopsied, 175.)

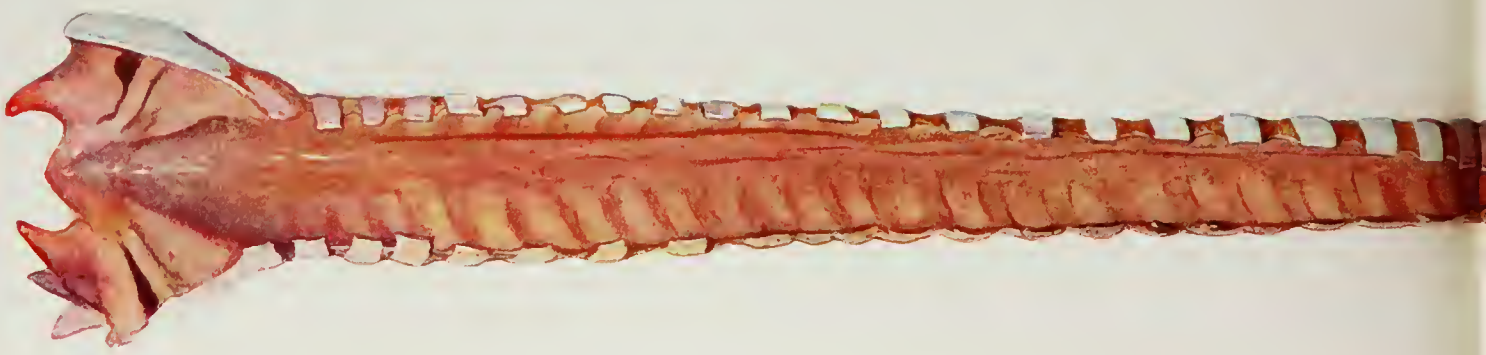
Group II. *Animals dying 2 to 5 days after gassing, "delayed death."* (Number autopsied, 46.)

Group III. *Animals dying 5 to 15 days after gassing.* (Number autopsied, 26.)

Group IV. *Animals dying or killed, 15 to 193 days after gassing, "chronic or recovered cases."* (Number autopsied, 79.)

In amplification of the figures just given Table I shows the number of animals coming to autopsy daily up to the 15th day after gassing and the total number of those living longer.

It is seen that a majority of the animals autopsied died within the first 24 hours after gassing, 172 out of 270, or 64 per cent., and that the number diminishes steadily with the time after gassing except that on the fourth day there was an increase over the third day.



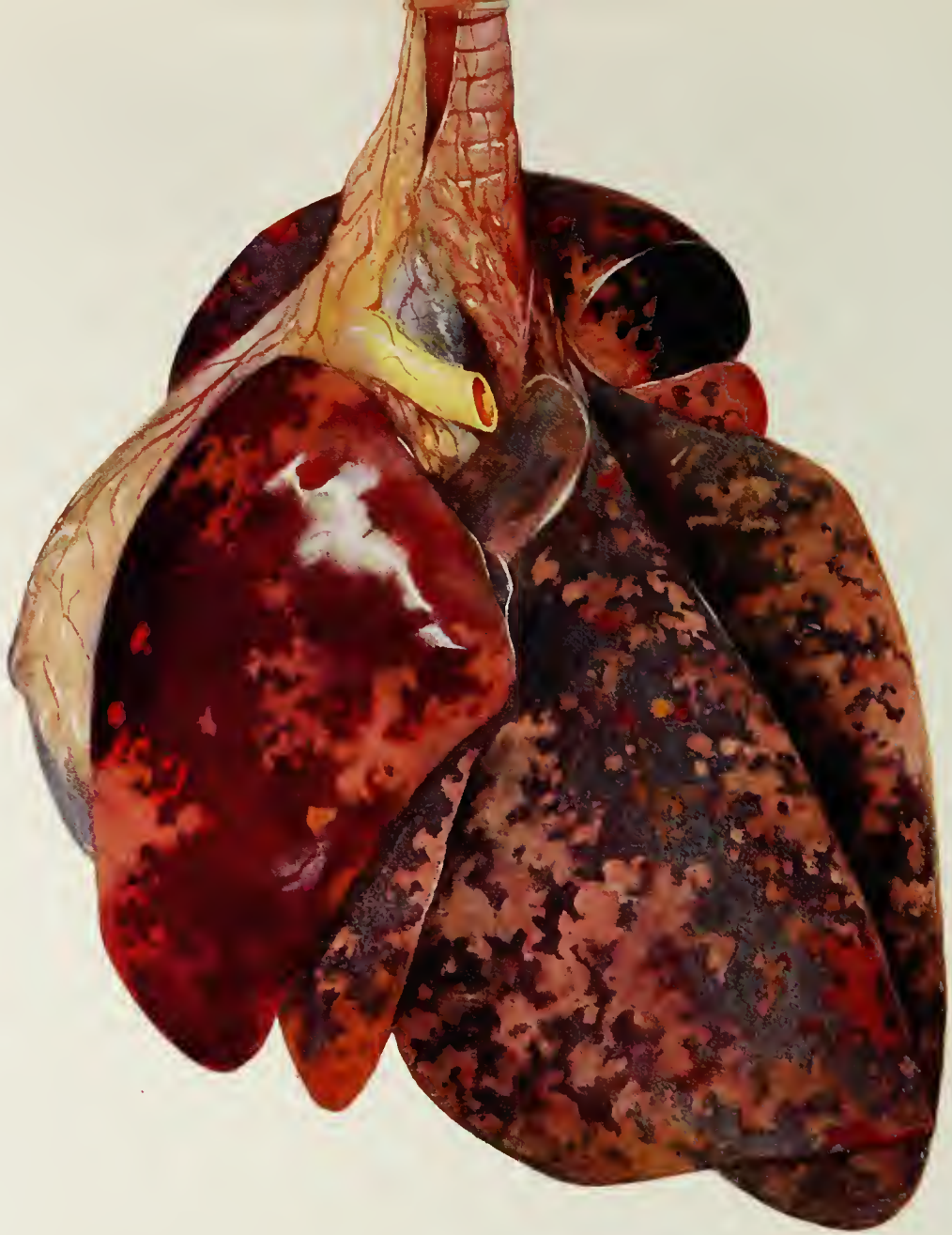


PLATE II

FIG. 1: TRACHEA AND LUNGS OF DOG DYING 12 HOURS AFTER GASSING.
THERE IS EXTREME EDEMA, CONGESTION AND CYANOSIS OF
THE LUNGS WITH PATCHES OF ACUTE EMPHYSEMA.
TRACHEAL MUCOSA IS NECROTIC AND
COVERED BY A STICKY EXUDATE.

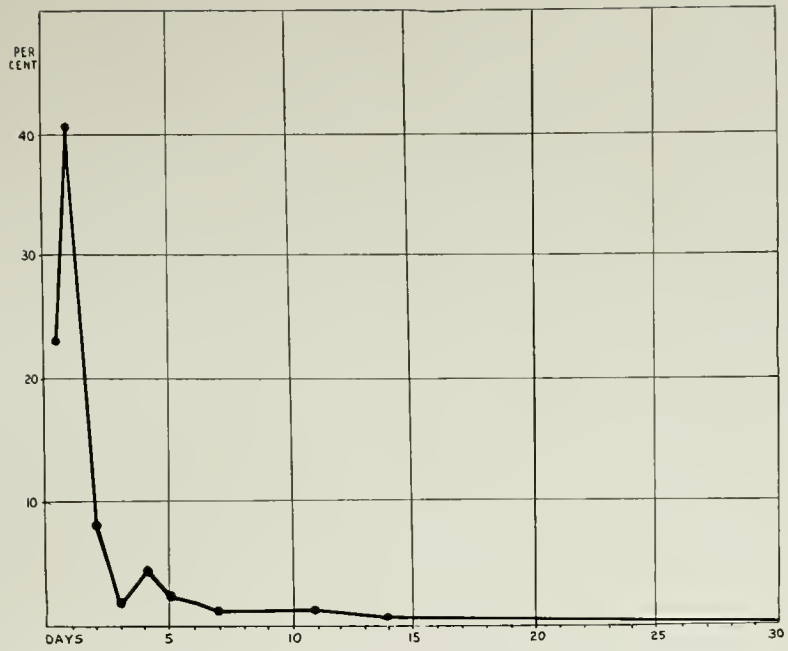


CHART 1. HEIGHT OF CURVE IS REACHED IN FIRST 24 HOURS. THERE IS A SECONDARY RISE ON 4TH DAY DUE TO PNEUMONIA.

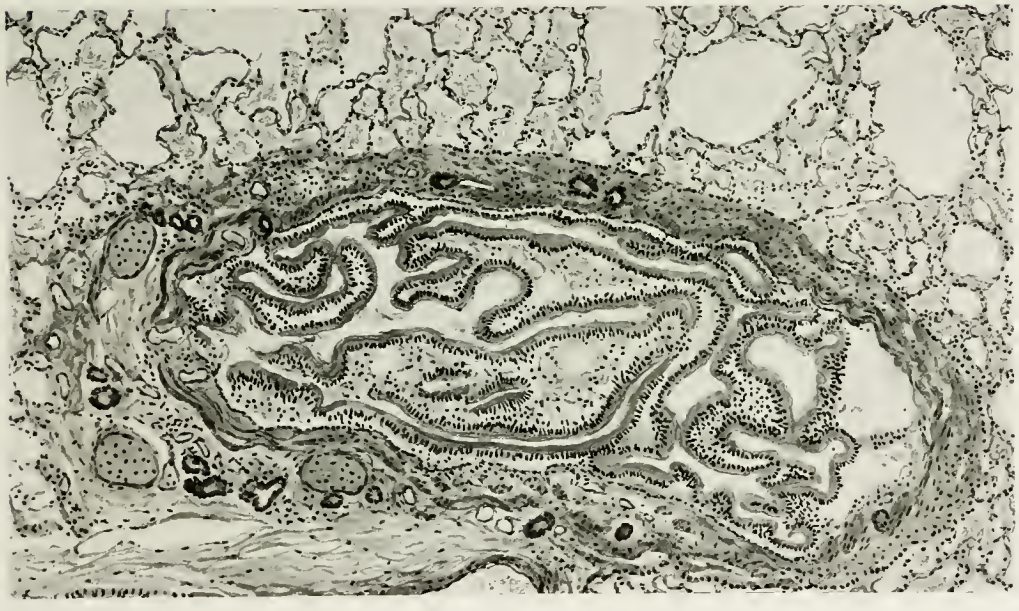


FIG. 3. LUNG OF DOG KILLED 3 HOURS AFTER GASSING. SHOWS LARGE BRONCHUS, EPITHELIUM OF WHICH IS "COOKED" AND DESQUAMATING. LUMEN IS FILLED WITH SHEETS OF MUCOSA WHICH HAVE SLOUGHED AWAY FROM A BRONCHUS HIGHER UP. NOTE ABSENCE OF INFLAMMATORY REACTION AT THIS STAGE.

An explanation for this secondary increase will be suggested in the discussion of the Group II cases.

The curve in Chart I brings out this rise better than the figures in the table. It should be explained, however, that the autopsies forming the basis of this chart comprise dogs from a number of different experiments in which different concentrations of gas were used. Treated and untreated animals are included. The curve is therefore not to be regarded as showing the actual death rate by periods but the relative number of dogs from these different periods which we have studied.

The curves showing death rate by periods after exposure to different concentrations of chlorine will be found in papers by Underhill and his co-workers, to be published shortly.

GROUP I. *Animals Dying During First 24 Hours After Gassing.*

Of the 175 dogs belonging to this group, 62 died within 12 hours after gassing, 3 were killed in the first 2 hours. The gross anatomical findings in animals belonging to this group are practically the same. Such differences as are noted are largely those of degree. In general it may be stated that the pathological changes, both in the respiratory system and elsewhere, become progressively more marked as death is delayed up to 24 hours. This point will be emphasized later in the course of the discussion.

Body: As a rule the eyes are reddened (acute conjunctivitis) with often a slight mucopurulent discharge. A frothy fluid exudes from the mouth; and if the animal is allowed to lie for a short period after death, a pool of fluid accumulates at the head. Post-mortem changes are conspicuous in many cases even among those examined within 3 to 4 hours after death. Decomposition is often quite advanced after 5 to 6 hours. It is associated in almost every case with an invasion of the tissues, especially the liver, by the gas bacillus. The liver even after only 2 to 3 hours is often speckled with gaseous patches of varying size. That autolytic processes go on more rapidly after death in gassed than in non-gassed animals is very evident. The explanation for this acceleration is not clear, although it might be suggested that the normal ferment inhibiting substances may be in some way affected or possibly destroyed in the course of gassing.

Abdomen: The abdominal organs show a very marked congestion. This is particularly true of the liver. The congestion is less marked in the kidneys and spleen. The vena cava is greatly dilated; its larger branches are similarly engorged. This picture is undoubtedly dependent upon the changes in the thoracic viscera, which will be emphasized later. The peritoneal surfaces are smooth, and there is no accumulation of ascitic fluid.

Thoracic Cavity: The lungs are very voluminous. They tend to overlap in the median line. The pleural surface does not show the usual wrinkling of the normally collapsed organ, but is now stretched, glossy, and semi-translucent. The tissues of the anterior mediastinum are markedly edematous. This edema involves the tissue around the great vessels, the thymus gland, and peribronchial structures. There is usually an excess of clear fluid in the pleural cavity. This is not so often seen in the pericardial cavity.

Heart: The heart is quite regularly dilated, often markedly so. Very frequently the apex is bifid and the right side projects further than the left. All chambers of the heart share in the dilatation, although it is much more marked on the right than on the left. If the animal is autopsied shortly after death, the blood is usually fluid; later, clotting takes place. The clots in the animals that have survived only a few hours after gassing are usually black cruor in type. In animals that live from 10 to 24 hours the clot becomes progressively

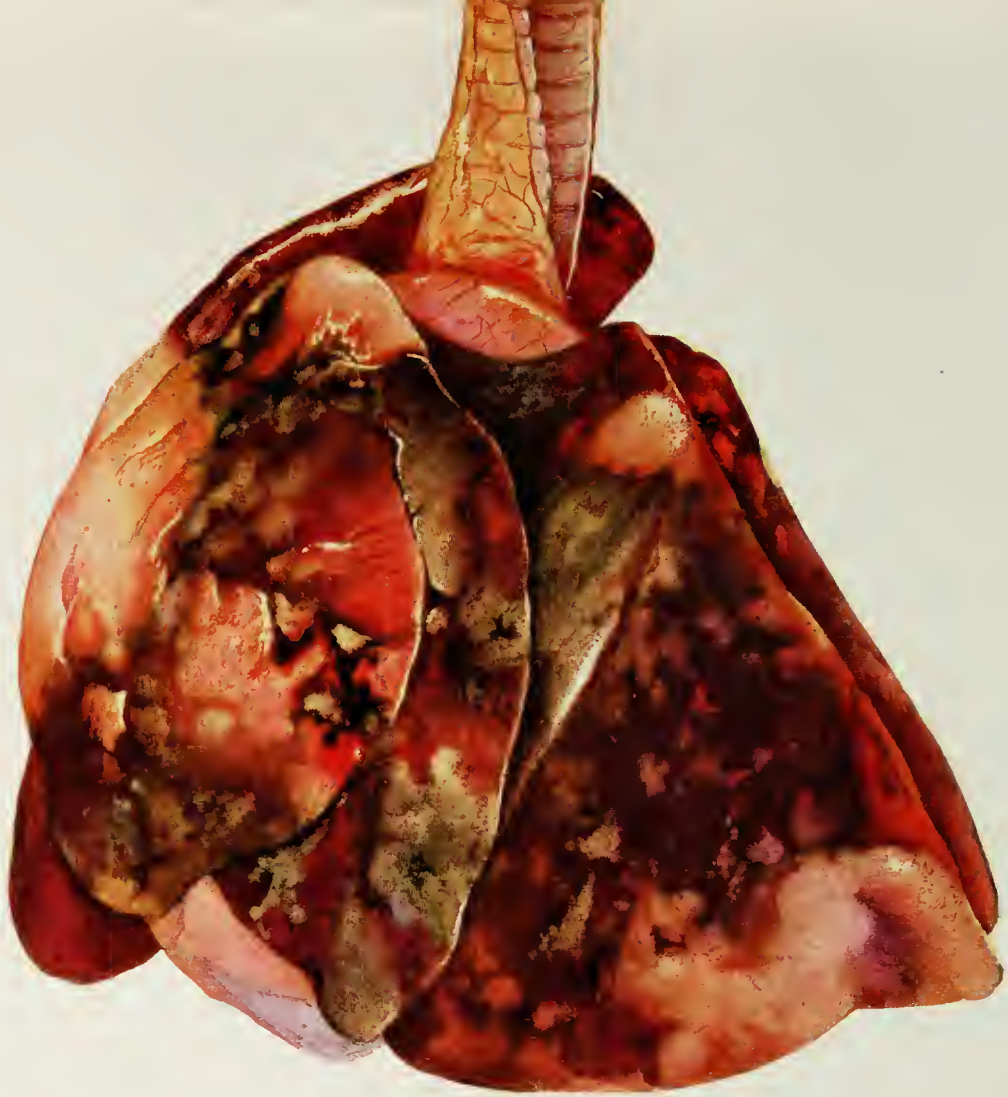


PLATE III

FIG. 2: TRACHEA AND LUNGS OF DOG DYING 5 DAYS AFTER GASSING. THERE IS A MEMBRANOUS TRACHEITIS AND A WIDESPREAD CONFLUENT BRONCHO-PNEUMONIA, AND MEMBRANOUS TRACHEITIS.

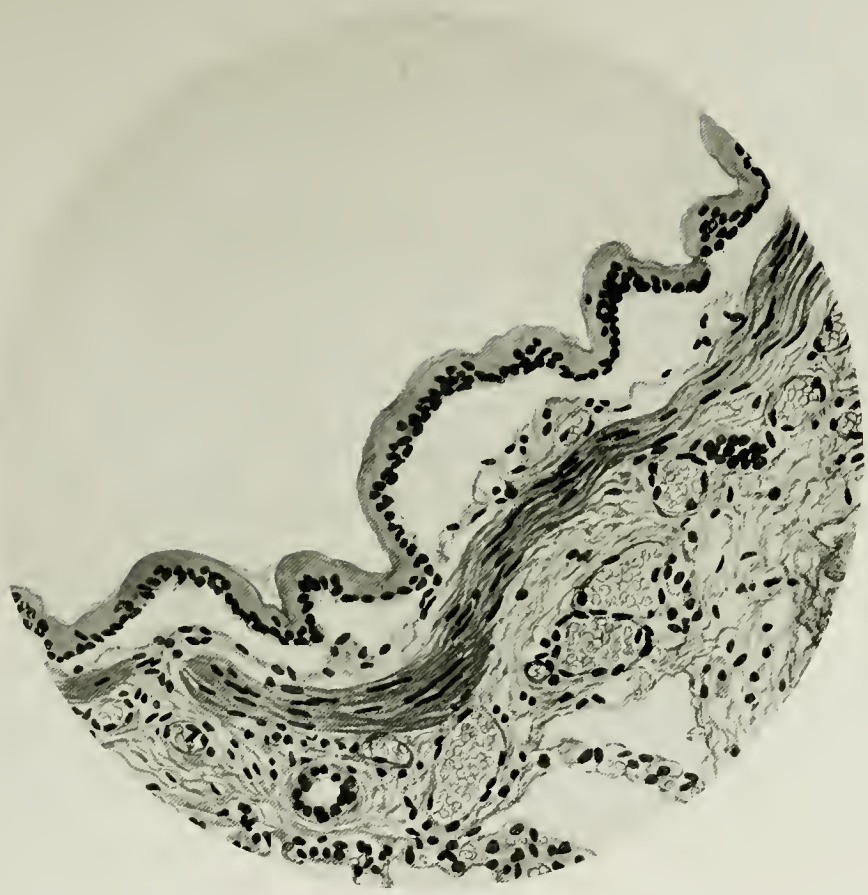


FIG. 4. HIGHER MAGNIFICATION OF BRONCHIAL WALL FROM CASE ILLUSTRATED BY FIG. 3.

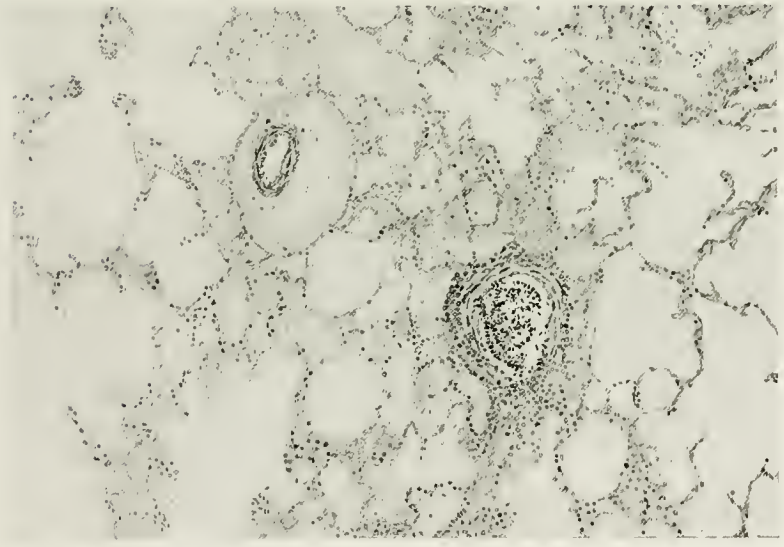


FIG. 6. ANOTHER FIELD IN LUNG ILLUSTRATED BY FIG. 3. A SMALL BRONCHUS IS COMPLETELY OCCLUDED BY SLOUGHED EPITHELIUM. THE OUTER COAT OF A SMALL ARTERY IS EXTREMELY EDEMATOUS.

more translucent and yellow, that is, of the typical chicken fat quality. Aside from the dilatation of the chambers previously mentioned and a thinning of the walls of the heart proportionate to the dilatation, there is nothing abnormal in the cavities—auricles, or ventricles. The endocardium as a rule is smooth and glistening, but occasionally on both the valvular and mural endocardium brilliant red spots (sub-endocardial hemorrhages) are found, which may be irregularly stellate in form or definitely rounded or oval. Very rarely the endocardium over the hemorrhagic spot is roughened. We observed a single instance of a thrombus over such an area on the tricuspid valve.

Trachea, Bronchi, and Lungs: As the trachea and bronchi are opened, a great quantity of frothy fluid pours out. The mucous membrane of the trachea is reddened, and the vessels deeply injected. In animals that survive only a few hours the surface is quite smooth though somewhat opaque, with a loss of the normal gloss and translucency. Later, there is a sticky membraneous exudate over the surface. This is generally quite tenacious and is removed with difficulty. The gross picture of the large bronchi is practically identical with that of the trachea (Fig. 1).

The *lungs* are very voluminous, filling the thoracic cavity. They retain their shape after removal, even after considerable fluid has escaped from the bronchi, and they collapse only slightly and gradually after sectioning. They are more or less doughy throughout, with faint crepitation in places. The color is brilliant and variegated. The background is a red of deep, rich quality with a mixture of blue, giving in general a purple hue to the whole. There are also lighter colored patches, most numerous toward the margins of the upper lobes, but scattered generally through all lobes. These lighter areas are slightly elevated, and on close inspection are seen to be foci of acute emphysema, although in some places the air of the distended alveoli has been replaced by fluid. The darkest colored parts of the lung are depressed rather than elevated, and are obviously partially collapsed areas (Fig. 1).

The *pleura* is smooth and shiny. An acute pleurisy is never seen at this early period. Sub-pleural hemorrhages are, however, frequently encountered. They are sometimes numerous and large.

When the lung is sectioned, a tremendous amount of fluid escapes. The cut surface is red and more or less translucent. There is very little air in the bronchi and still less in the lung tissue proper.

The larger blood vessels stand out prominently everywhere, owing to the presence about each of a relatively wide watery zone (perivascular edema). This may measure as much as 4 mm. in diameter.

In animals dying within a few hours after gassing, there is no gross evidence of an inflammatory reaction in the lung other than the presence of the serous exudate just described. Later on, in animals that have survived 10 to 24 hours after gassing, small areas of pneumonic consolidation can sometimes be made out, though with difficulty, owing to the co-existing edema and congestion, which dominate the picture. When visible these tiny pneumonic patches appear on section as slightly granular, reddish, dry areas, which have a lobular distribution. A well-developed pneumonia is not often seen in the first 24 hours. As shown in Table II, none could be demonstrated microscopically in the first 12 hours and in only about 25 per cent. in the second 12 hours.

The *blood vessels* at the hilus of the lung appear dilated, but in no instance have we found thrombi within them.

The *bronchial lymph glands* are large and, on section, soft and succulent.

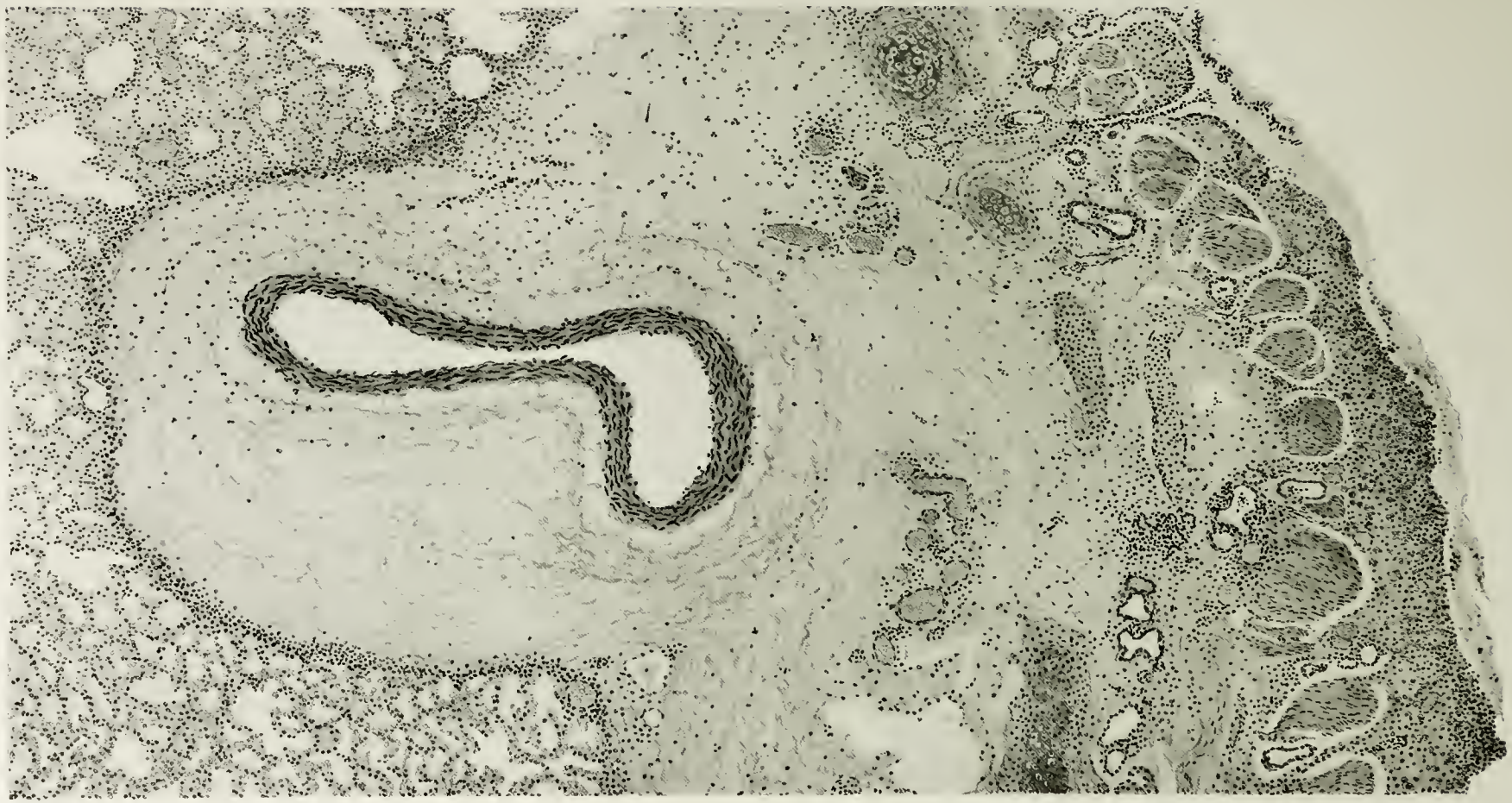


FIG. 5. WALL OF BRONCHUS OF DOG DYING 10 HOURS AFTER GASSING. EPITHELIAL COVERING HAS SLOUGHED OFF, AND AN ACUTE NECROTIZING INFLAMMATORY REACTION IS PRESENT INVOLVING THE ENTIRE WALL AND EXTENDING INTO THE PERI-BRONCHIAL TISSUES. NOTE THE EXTREME EDEMA, MOST STRIKING IN THE SHEATH OF A NEIGHBORING ARTERY. THE ADJACENT LUNG TISSUE SHOWS CONGESTION AND EDEMA.

Microscopic Findings.

Description of the microscopic appearance of the tissues in this group of animals will be confined chiefly to changes in the respiratory tract. The histological changes in the other tissues are very inconspicuous. The capillaries of the liver and other abdominal viscera are dilated, and the cells of the liver and kidney exhibit a moderate degree of parenchymatous degeneration. These minor lesions are obscured, especially in the liver, by the rapid post-mortem autolytic changes referred to above.

The microscopic changes in the *trachea* and the *larger bronchi* are such as might be expected from the gross appearance. The mucous membrane, even in cases of death within 2 hours after gassing, looks coagulated with deeply staining nuclei and homogeneous cytoplasm. It is often raised in blister-like fashion from the submucosa, and sheets of it are found lying in the trachea and bronchi (Figs. 3 and 4). When a longer period has elapsed after gassing the mucous membrane may be completely sloughed away or if still attached show more or less nuclear and cytoplastic disintegration (Fig. 5). In the very early stages, that is, 2 to 4 hours after exposure, the other coats of the bronchi show great engorgement of vessels and more or less edema but no cellular infiltration. There takes place very soon, however (6 to 12 hours), a marked and rapidly progressive inflammatory reaction with an outpouring of leucocytes and fibrin (Figs. 5 and 7). These elements mixed with necrotic epithelium constitute the tenacious membranous exudate seen in the gross specimen. The cells of the exudate are chiefly polynuclear leucocytes with a number of red blood cells. They appear not only in the submucosa but all through the tracheal and bronchial walls and are often scattered about in the edematous peribronchial tissues and in the vessel sheaths outside (Fig. 5).

Although there is practically everywhere a coagulation of the exposed layer of ciliated epithelium, there are many places in which the deeper syncytial layer of cells is apparently uninjured. Their survival probably explains the early rapid regeneration of the epithelium found in the subacute and chronic stages (Fig. 8).

The changes in the *smaller bronchi* are very much the same as in the larger ones. Many are completely filled with mucus and edematous fluid, and here and there one sees a bronchiole completely plugged by sheets of necrotic epithelium aspirated from the trachea and larger bronchi where sloughing has taken place (Fig. 6). Occlusion of the smaller bronchi produced in this way is probably important in bringing about the changes in the lung, particularly emphysema and atelectasis, to be discussed later. Another and probably more important process of bronchiolar obstruction, namely, muscular spasm, can be demonstrated in sections. This is not seen in the larger bronchi supported by a cartilaginous wall but occurs in the smaller bronchioles as far as the atrium of the alveolus itself. In the most acute animals, that is, those dying within a few minutes to an hour after gassing, the bronchioles are often markedly dilated, so that their normal corrugation is lost; but in later cases it is possible to demonstrate a definite constriction near the atrium, which completely closes the bronchial tubes. In other instances the atrium as well as the bronchus appears to be dilated, and the alveoli associated with such a bronchus have very large lumina.

A large percentage of animals show in the bronchi and smaller bronchioles a picture quite different from that just described. Instead of a uniform dilatation there are alternate dilatations and constrictions (Fig. 9). In places the mucous membrane is markedly corrugated and the opposite walls are in contact; the whole structure has a corkscrew-like appearance. In the areas of constriction the musculature of the bronchiolar wall is

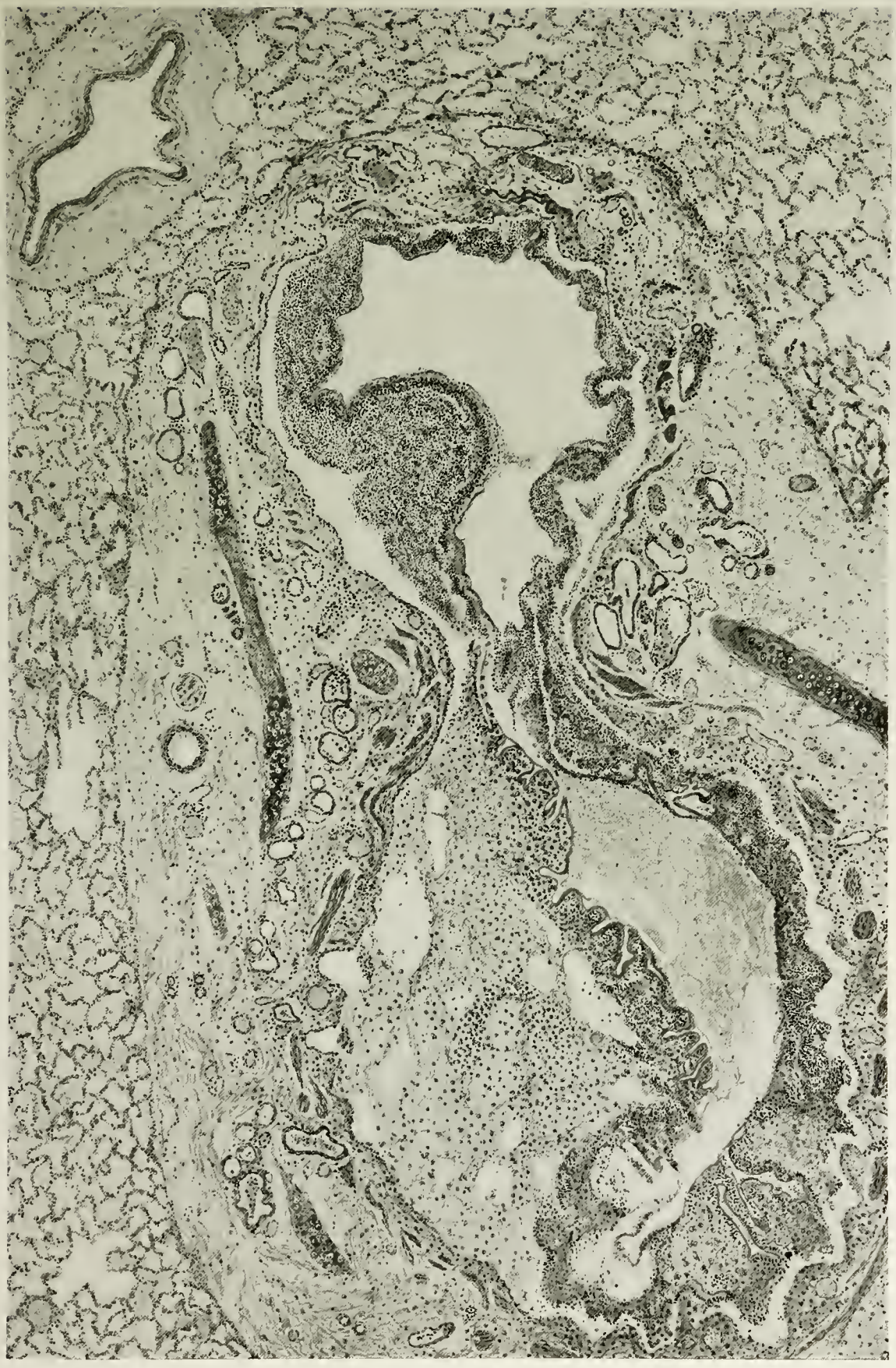


FIG. 7. NECROSIS OF BRONCHIAL EPITHELIUM, WITH ACUTE INFLAMMATORY REACTION, IN DOG DYING 24 HOURS AFTER GASSING.

distinctly contracted. This bronchiolar contraction is associated with different changes in the alveoli. In some instances the atrium of the alveolus is similarly contracted, but the alveoli are dilated with their walls much thinned out, a picture of extreme emphysema. In other instances the alveoli are not dilated and then the bronchiolar constriction is not as complete.

Lungs: The microscopic changes in the lung tissue itself are even more varied and striking than those of the bronchi, upon which, however, the pulmonary changes as suggested before, are undoubtedly to a large extent dependent. In the whitish elevated patches seen grossly the alveoli are found to be greatly distended. The alveolar walls are markedly thinned out and often ruptured with the formation of large air sacs from whose walls project at intervals the bulbous tips of the torn septa (Figs. 10 and 11). Alternating with these patches of acute emphysema are areas generally much larger in extent, in which the capillaries are widened and tortuous and the alveolar walls correspondingly thickened. The alveolar spaces here are reduced in size and filled more or less completely with edematous fluid. This fluid is sometimes so rich in albumin that as a result of a coagulation by the fixative, it resembles the colloid material of the thyroid. Usually, however, it appears as a finely granular pink staining precipitate (Fig. 11).

In practically every case more or less fibrin is present in the edematous fluid, though it is in and on the alveolar wall that fibrin is more regularly found, often in large quantity (Fig. 13). It is here, we believe, that its presence has most importance in interfering with the normal flow of blood through the organ thus increasing the strain on the heart.

The *blood vessels*, capillaries especially, in the lung in this early period are very regularly dilated. While it is possible that there may be in the very beginning a contraction of the musculature of the blood vessels similar to that described in the bronchial wall, this cannot be demonstrated. Thrombi in the vessels have been seen in no instance. The post-mortem clots present are, however, very often quite rich in fibrin.

We have not been able to recognize an agglutination of the red blood cells in the capillaries (agglutination thrombi) described by Bunting (unpublished communication). The blood flow through the capillaries is undoubtedly seriously impeded, as Klotz has emphasized; but as suggested in a previous paragraph, an explanation for the obstruction is found in the presence in many places of a thick layer of fibrin on either side of the capillary, that is, on the alveolar wall, with numerous strands running across the vessel connecting the two layers (Fig. 13). This condition is no doubt produced by an immediate clotting of the plasma (edema fluid) as it passes out of the capillary. The amount of fibrin in the very early cases is small. It is seen in largest quantity in dogs living 1 to 3 days.

A focal *hyaline necrosis of the alveolar walls* constitutes perhaps the most interesting feature of the microscopic findings in the lungs. These necrotic foci are distributed rather irregularly through the lung. They are sometimes very numerous and fairly large, occupying more than a field under the lower power of the microscope. In other cases they may be scarce and small, or entirely lacking. The characteristic, homogeneous, cooked appearance of the structures in these areas is very well shown in Figures 10 and 12. It is noted that the center of the necrotic focus is practically always an atrium, with sometimes a bit of the bronchiole included. The dead tissues are generally free of blood, the capillaries being apparently obliterated by the swollen dead alveolar walls. Red blood cells, however, are often seen scattered through the alveolar spaces in the dead patches. Sections prepared with hematoxylin and eosin show the dead walls stained a deep red, the nuclei pyknotic or absent;

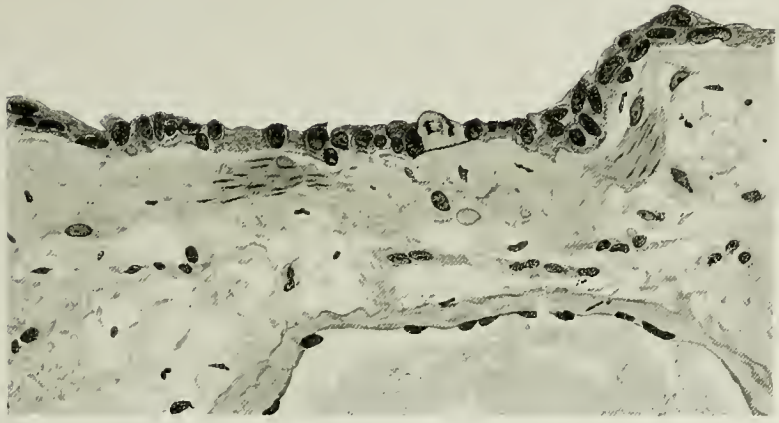


FIG. 8. REGENERATION OF BRONCHIAL EPITHELIUM 4 DAYS AFTER GASSING.

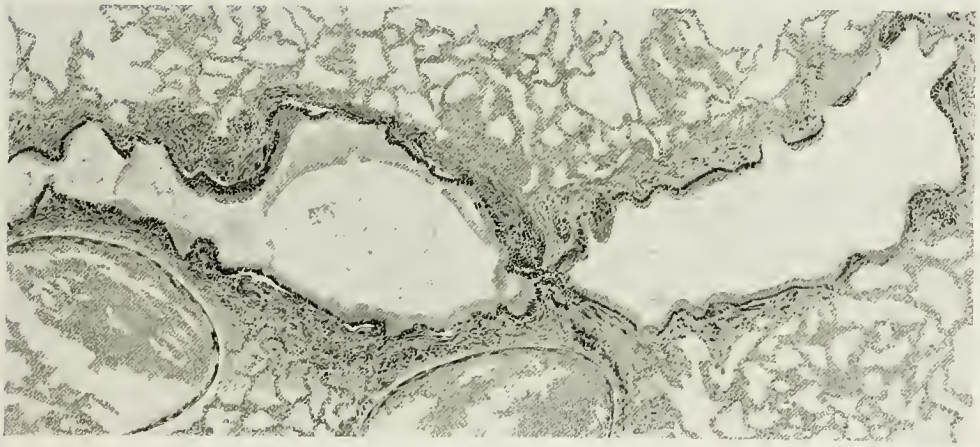


FIG. 9. IRREGULAR CONTRACTION OF BRONCHUS; DEATH IN ACUTE STAGE.

with the Weigert fibrin stain the dead tissue tends to take a violet hue. There can be little doubt that this lesion is produced by the direct action of chlorine gas. The question will be taken up again in the general discussion of the pathogenesis of the lung lesions.

Inflammatory Reaction in the Lung: The extreme engorgement of the vessels of the lung and the outpouring of serum and fibrin already mentioned, ean be interpreted, and we are inclined to think should be interpreted, as of an inflammatory nature; certainly the migration of polynuclear leucocytes, early seen in increased numbers in the alveolar walls and soon thereafter free in the alveolar spaces gives proof that an inflammatory process is going on. While the capillaries everywhere show an increased number of polynuclears, it is in the walls of the smaller bronchi and bronchioles and the adjacent alveoli that focal accumulations of these cells arc first noted (Fig. 14). This inflammatory reaction has been seen as early as two hours after gassing, and is found more regularly in dogs surviving more than six hours.

In Table II the increase in cases showing a definite inflammatory reaction in the lungs runs parallel with the time after gassing. For example, in dogs dying within 12 hours after gassing only 18 per cent. showed pneumonia, whereas those dying between 12 and 24 hours showed 54 per eent. and the pereentage of pneumonia reaehes 100 per cent. in those dying between 5 and 14 days. It may be explained that in the preparation of Table I only cases studied histologically are included, and since in many instances sections from only 2 or 3 bloeks of lung tissue were examined, it is possible that a considerable number of early pneumonias may have been overlooked. In other words, the incidence of pneumonia in this early group of dogs as well as in the other groups is probably larger than our figures would indicate, owing to the fact that the margin of error extends only in the direction of missed or overlooked cases. The question of the cause of this acute inflammatory reaction, acute bronehiolitis, or early pneumonia, as it may be termed, whether bacterial or chemical, will be taken up in a later paragraph.

SUMMARY

The salient features of the pathology of dogs dying within the first 24 hours after gassing with chlorine may be summarized as follows:

1. A severe injury to the mucous membranes of the upper respiratory tract leading to superficial sloughing of the mucosa, and followed by a membranous tracheitis and bronchitis; foeal areas of necrosis in the lungs.

2. Irregular dilatation and eontraction of the bronchi resulting in alternating patches of acute emphysema and atelectasis in the lungs.

3. Extreme congestion and edema of the entire respiratory tract including peribronchial tissues and the sheaths of the large blood vessels.

4. An aeute inflammatory reaction beginning within a few hours and devcloping into pneumonia.

Group II. *Animals Dying 2 to 5 Days After Gassing.*

There are 46 dogs in this group of which 25 died on the second, 8 on the third, and 13 on the fourth day. Among these the gross pathologieal picture differs slightly from that in the members of Group I. The four- and five-day dogs are more easily differentiated.

In general, it may be stated that eye changes are not present and usually fluid does not escape from the mouth. The abdominal organs are not as regularly congested as in

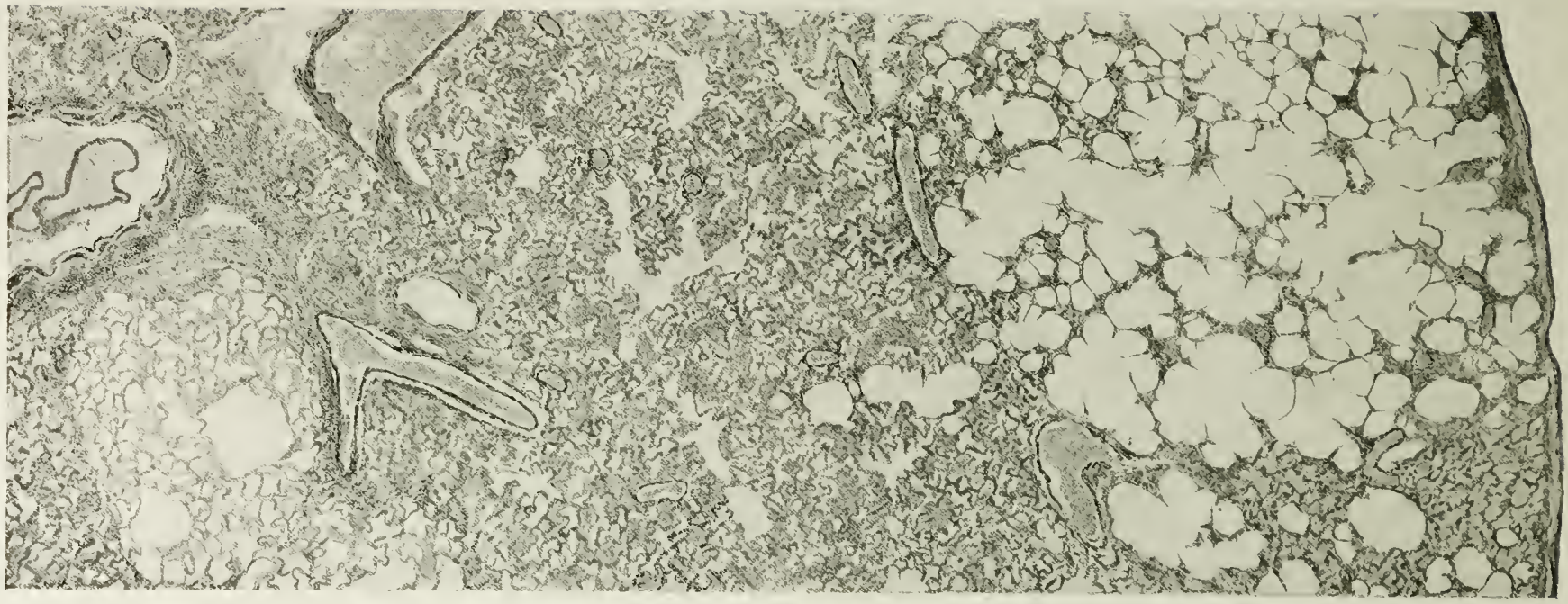


FIG. 10. LUNG OF DOG DYING 12 HOURS AFTER GASSING. NOTE EMPHYSEMATOUS AREA ON RIGHT BENEATH PLEURA. COLLAPSED LUNG TISSUE ON LEFT. ON EXTREME LEFT THERE IS A BRONCHUS WITH SLOUGHING MUCOSA, AND BELOW THIS AN AREA OF FOCAL NECROSIS WITH "COOKED" ALVEOLAR WALLS.

Group I, and the congestion when present is not extreme. The vena cava though dilated, does not present the same degree of engorgement which it and its branches show in animals dying earlier. The lungs are voluminous, but as a rule not uniformly so.

There is still some free fluid in the thoracic cavities and some edema of the mediastinal tissues, particularly of the thymus and peribronchial structures.

The *heart* is usually dilated, sometimes to an extreme degree. Chicken fat clots form molds of the cavities. The cruor clots seen in the animals dying in earlier periods after gassing are absent.

Respiratory Tract: The picture in different lobes of the lung varies somewhat. Occasionally, a large, homogeneous, reddish lobe is found, which is firm and nodular and does not crepitate. In other instances, similar, easily palpable patches may be felt scattered through all parts of the lung. It is common to find this latter distribution in the relatively acute stages, that is, on the second and third days. The remainder of the lung tissue has a translucent gelatinous appearance with occasional reddish brown areas of hemorrhage on the pleural surface similar to those described in animals of the first group. The amount of frothy fluid that escapes from the bronchi varies with the different lobes, very little coming from the pneumonic parts.

While animals dying on the second and third day show an extreme edema, it is the rule to see a subsidence of the edema after the first 48 hours. The peritracheal tissues are edematous, and even to the naked eye, the sheaths about the vessels stand out clearly, but are never as widely distended as in the earlier cases.

The *trachea* and *bronchi* show, as in the earlier stages, extreme congestion, obscured somewhat by the presence of a muco-purulent exudate. These changes are especially marked in the smaller bronchioles. When traced out, bronchioles are found frequently distinctly dilated even near the surface of the lung, but it is difficult to determine from gross examination alone the extent of this dilatation.

One or more lobes of the lung may be uniformly consolidated, and dry and coarsely granular on section, the picture of a lobar pneumonia; much more often, however, the consolidation is patchy or lobular in distribution (Fig. 2).

The lobes or portions of lobes which are not consolidated are similar in appearance to the lungs of Group I dogs. The areas of emphysema and atelectasis are even better defined, especially in the two- and three-day animals. In almost all instances the smaller bronchi contain pus, and not infrequently on slight pressure a yellowish creamy material escapes from them. Sometimes the yellowish material is not confined to the lumina of the bronchi, and seems to extend into the surrounding alveoli.

Microscopic Changes: The histological changes in this group of animals are, as might be expected, an exaggeration of those in the first group, especially as regards the inflammatory reaction. In all, the pneumonic process overshadows the rest of the picture. The pneumonia may be either lobar or lobular in type, but in nearly every case the microscopic picture is that of a lobular or broncho-pneumonia (Fig. 16). The alveoli are packed with white blood cells, a few red blood cells, and, generally, only a small amount of fibrin. The alveolar walls vary in their appearance. In places where the exudate is less marked, they are wide, and their vessels dilated. In the areas where the leucocytic infiltration is most marked, they are vague and more or less obscured by the abundant exudate. Now and then, one sees the alveolar wall broken down with abscess formation. Most of these abscesses originate in suppurating bronchi.

Alveoli which are not involved in the more advanced inflammatory process may be

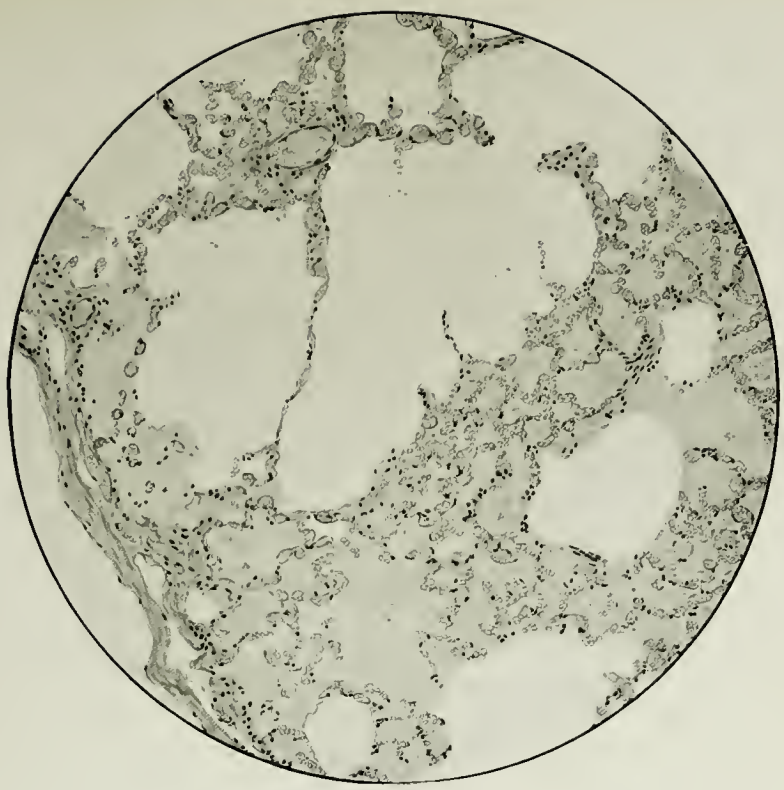


FIG. 11. LUNG OF DOG DYING IN ACUTE STAGE AFTER GASSING WITH CHLORINE. SHOWS EXTREME CONGESTION, MODERATE EDEMA, AND ALTERNATING PATCHES OF ACUTE EMPHYSEMA AND PARTIAL ATELECTASIS. CONGESTION AND EDEMA ARE MOST PRONOUNCED IN COLLAPSED AREAS.

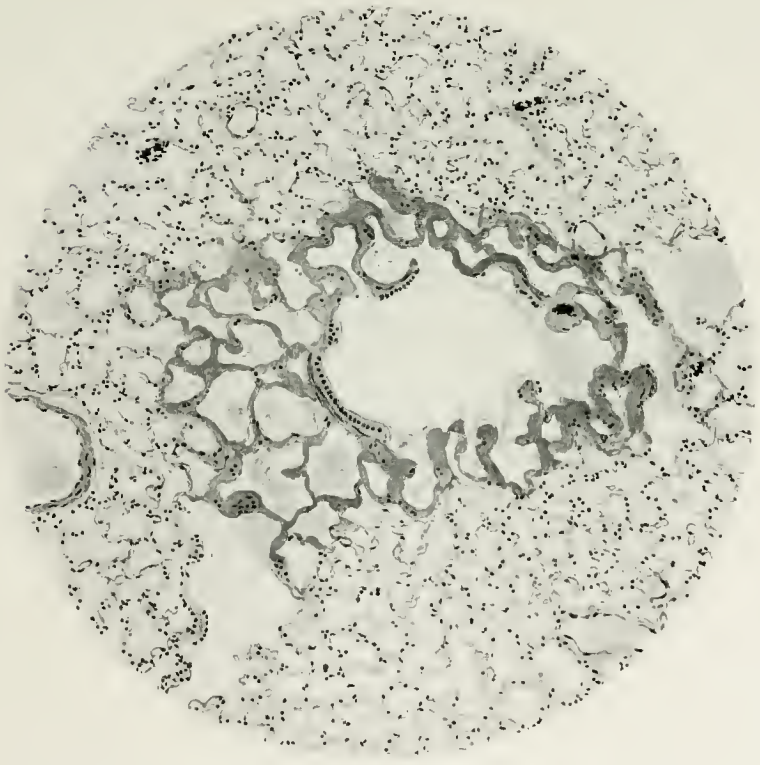


FIG. 12. FOCAL NECROSIS IN LUNG OF DOG DYING 6 HOURS AFTER GASSING. THE ALVEOLAR WALLS ABOUT AN ATRIUM ARE HYALINIZED AND STAINED DEEPLY WITH EOSIN. SOME EDEMA IS NOTICED IN THE ALVEOLAR SPACES.

filled with edematous fluid. They vary greatly in size. In many instances they are tremendously dilated, the picture of an extreme grade of emphysema. In other areas in the same lobe they may be collapsed. These alternating patches of emphysema and atelectasis are found not only at the surface of the lung, where they are most conspicuous, but also throughout the substance of the organ. In an effort to explain the difference in the degree of distension of the alveoli, careful study of the bronchi has been made.

In some instances a bronchus is seen to be plugged by a small mass of exudate, but the most striking change is focal constriction of the bronchioles, described in Group I. The bronchial constriction often extends even to the atrium of the lung; then a sudden dilatation may occur where the atrium opens into very large and very thin walled alveoli, suggesting that the contained air is under more or less tension. In the areas of atelectasis, the bronchi seem to be more completely constricted or more fully plugged with mucus, but from a study of microscopic sections alone it is difficult to say just what relations the bronchiolar changes bear to those in the lung parenchyma. A reconstruction of the organ might answer this question.

The bronchi also show inflammatory changes; the exudate, sometimes beneath the mucosa, but most frequently in the lumina, is made up largely of pus cells. The smaller bronchioles are filled with exudate composed chiefly of polynuclear leucocytes mixed with desquamated cells, fibrin and mucus. The exudate may extend into the surrounding alveoli.

Regeneration of the bronchial epithelium constitutes an interesting feature of the microscopic picture in this group. The superficial layer of ciliated epithelium is nearly everywhere destroyed. This destruction is practically universal in the lungs of animals dying early (Group I). In those living longer, it is possible to find patches of relatively uninjured epithelium where folds in the mucosa protected it, and there are numerous places showing the deeper syncytial layer of epithelium well preserved. It is from these cells that the new mucosa is regenerated. An active proliferation of them is sometimes seen in two-day animals, but is most energetic around the four-day period, when several mitotic figures may be found in a single high power field.

The blood vessels, capillaries especially, are engorged, but the engorgement is not as marked as in Group I. In no instance were thrombi demonstrable in either the large or small vessels. The walls of the vessels, particularly the perivascular sheaths, show some edema. An inflammatory exudate of polynuclear leucocytes and fibrin, particularly the latter, is often seen in the edematous zone.

SUMMARY

The most important feature of this second group, which has been termed "delayed deaths," is the inflammatory process. The early reaction found in Group I cases evidently increases in intensity and develops into a lobar or lobular pneumonia. Not infrequently the pneumonia is complicated by abscess formation and gangrene. In some cases, areas of focal necrosis found in the earlier stages have broken down and are transformed into abscesses. But a majority of the pus cavities develop out of the necrotizing infection of the bronchi.

The picture of bronchiolar spasm, described before, is most pronounced in this group, and undoubtedly is responsible for the patchy emphysema and atelectasis, which constitute a most striking gross characteristic of the lung.

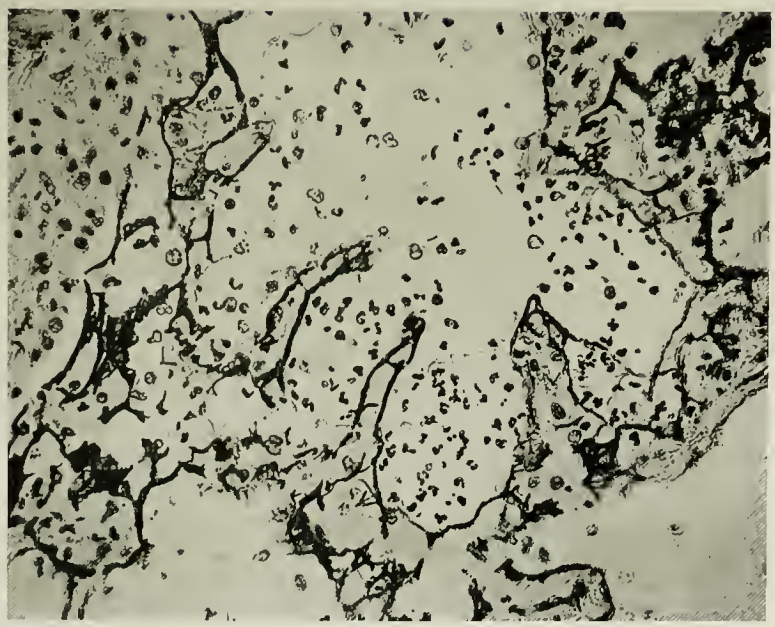


FIG. 13. FIBRIN IN ALVEOLAR WALLS 2 DAYS AFTER GASSING. A THICK LAYER IS SEEN COVERING THE SURFACE WITH STRANDS CROSSING AND OBSTRUCTING THE CAPILLARIES IN MANY PLACES. POLYNUCLEAR LEUCOCYTES ARE SEEN IN THE ALVEOLI.

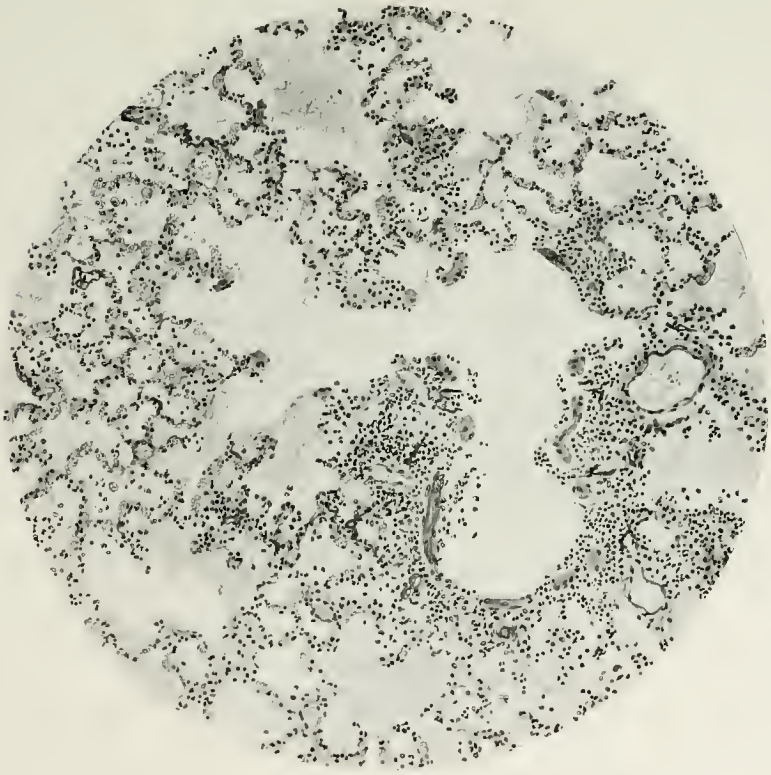


FIG. 14. ACUTE BRONCHITIS OR EARLY PNEUMONIA. THERE IS FOCAL ACCUMULATION OF POLYNUCLEAR LEUCOCYTES, WITH LITTLE FIBRIN AND FEW MONONUCLEAR CELLS IN AND ABOUT A BRONCHIOLE AT THE POINT OF ENTRY TO AN ATRIUM. THIS REACTION IS SEEN AS EARLY AS 4 HOURS AFTER GASSING.

GROUP III. *Animals Dying 5 to 14 Days After Gassing.*

This is an intermediate group which represents what might be termed a sub-acute stage. It is a connecting link between the early and late stages.

In each of the 26 animals belonging to this group, pneumonia was found at autopsy. In this respect the cases are like those in the preceding group, in which well-developed pneumonia was present in approximately 95 per cent. However, the character of the pneumonic process in this later stage is somewhat different; furthermore, other lesions, such as congestion and edema are absent or much less marked than in the cases succumbing in the earlier period.

On gross inspection, the organs show evidence of moderate anemia, with cloudy swelling and fatty changes in the liver and other parenchymatous organs. A certain degree of passive congestion may be present, but this is not conspicuous.

As in the earlier groups, the respiratory system contains the lesions which account for the death of the animal. The trachea and larger bronchi exhibit very much the same changes as are found in Group II. A purulent bronchitis is often present, especially in the consolidated parts of the lung. The lungs are partially collapsed; at least, they are not as voluminous as in the acute stage. Small, reddish patches, quite firm and nodular on palpation, are seen. Often an entire lobe or several lobes may be firmly consolidated. On the other hand, only small diffusely scattered nodules may be felt, which, on section, are gray and translucent, suggesting tubercles. A fibrino-purulent pleurisy sometimes complicates the pneumonia (see frontispiece).

There is very regularly more or less edema and congestion, generally more marked in the dependent portions of the lung.

Microscopic Findings: The most striking microscopic feature of this group is the tendency to organization of the inflammatory exudate, whether this be in the bronchi, the alveolar spaces, or in the septa. A well-developed broncho-pneumonia is present in a large majority of the cases. In a few instances it looks as though the infection were being successfully combated; that is, the débris is being cleared away, and the dead tissue replaced by granulation tissue.

SUMMARY

Death in this subacute stage is regularly due to pulmonary infection, pneumonia and bronchitis, the most striking feature of which is the tendency to organization. This process is cut short by the death of the animal; but the end result can be seen in the lesions found in the next group of chronic animals.

GROUP IV. *Animals Surviving 15 to 193 Days After Gassing.*

There were 79 animals in this group, of which 26 died and 53 were killed. Eleven of the 26 died between the 15th and 30th days, the remainder, during the succeeding five months. The majority of those killed were animals which had been kept on a farm for at least two months after gassing. Many of these dogs appeared to be in good health, but some were lean, sluggish, and of sickly appearance. The dogs that died were all poorly nourished, and some were very much emaciated.

The gross anatomical picture in these "chronic dogs," while not as striking as in the animals dying acutely, is, in certain respects, much more complex and interesting.

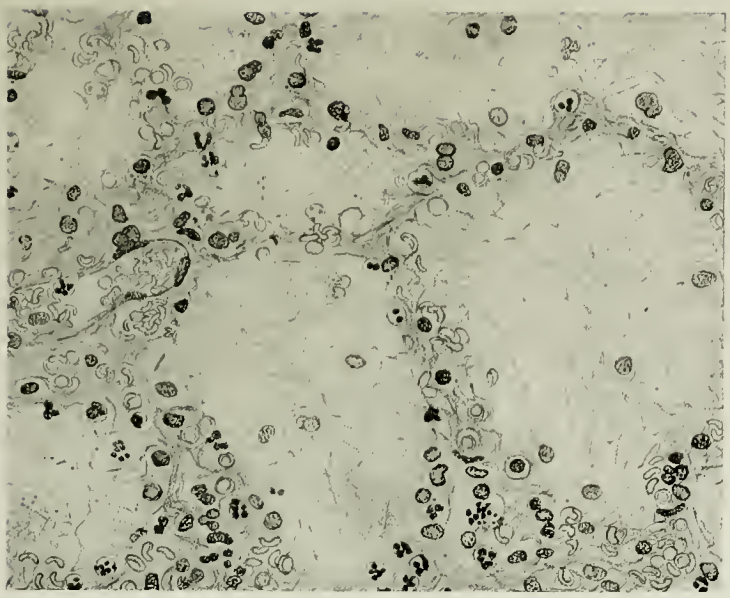


FIG. 15. "FIBRINOUS PNEUMONIA" IN DOG DYING 3 DAYS AFTER GASSING. THIS PICTURE IS THE EXCEPTION, THE PNEUMONIAS SHOWING GENERALLY ALVEOLI FULL OF CELLS WITH FIBRIN DEPOSITED CHIEFLY IN AND ON THE ALVEOLAR WALLS.

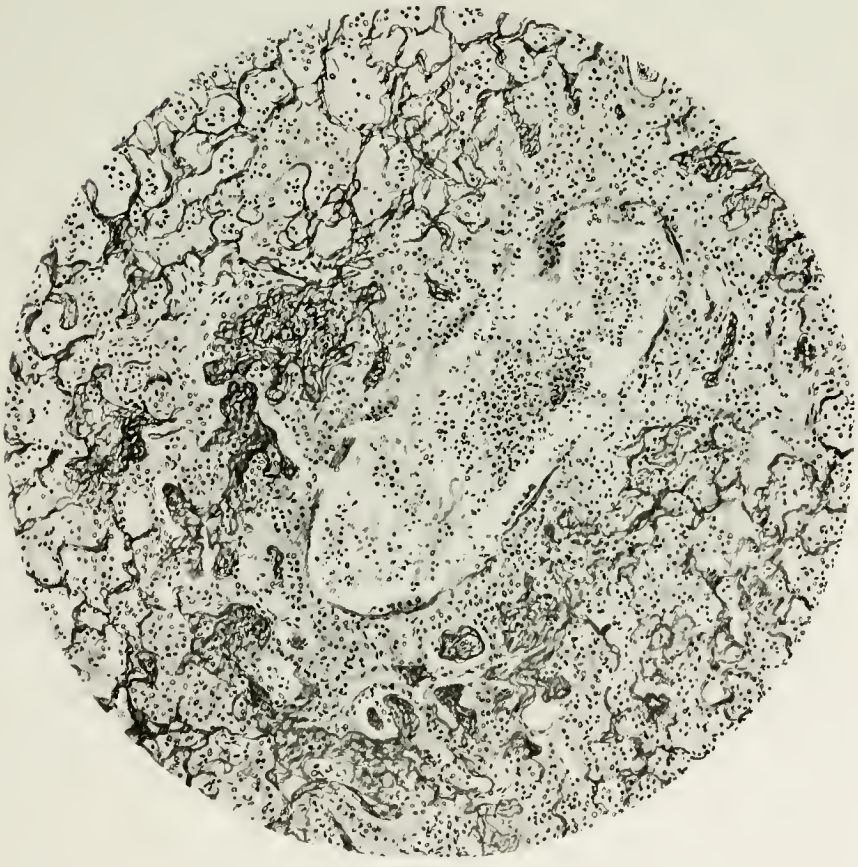


FIG. 16. EXTENSIVE BRONCHO-PNEUMONIA IN A DOG DYING 4 DAYS AFTER EXPOSURE. THE BRONCHUS IN THE CENTER HAS LOST ITS MUCOSA AND THE OUTER COATS ARE BEING BROKEN DOWN. THE ALVEOLAR SEPTA ARE OUTLINED BY THICK STRINGS OF FIBRIN, WHICH IS DEPOSITED IN THEM.

All organs of the body show a picture such as is generally associated with chronic infection. There is more or less pallor of the abdominal viscera, and often fatty changes in the liver and kidneys. The spleen is usually enlarged, has an increase in fibrous tissue and a very large amount of pigment in its pulp. The picture of acute passive congestion, which is so striking in the animals dying early, does not pass over into a chronic passive congestion.

The *pleura* is normal, with no excess of fluid in the cavities and no old adhesions. In view of the fact that an acute pleurisy is not seen in animals dying early after gassing, the entire absence of healed lesions is not surprising. On the other hand, an acute pleurisy was twice noted in these chronic dogs, and, in one case, a bilateral empyema was found. These were associated with a widespread, purulent bronchitis.

The *lungs* are not voluminous. As a rule they collapse well as the chest is opened, freely exposing the pericardium and heart. The collapse is not uniform, however. There is no edema of the mediastinal tissues and no fluid or other exudate in the trachea, except perhaps an excess of mucus. This is very pronounced in the bronchi.

The *heart* is little altered. There is no dilatation of the cavities and no microscopic change in the endocardial lining. In no instance have vegetations been found on the valves.

Lungs: The bronchi are not markedly changed, at least, not the larger bronchi; but the bronchioles, or what should be the smallest bronchial tubes, are often found to be thick walled, greatly dilated, and plugged with exudate. These changes in the bronchi are associated with definite lesions in the lung tissue proper. In a majority of the cases, the lungs present areas of atelectasis, maroon or brownish in color, while the rest of the lung is irregularly emphysematous, sometimes markedly so. Wherever atelectasis is found, it is associated with dilatation and plugging of the bronchi with muco-purulent material. The areas of emphysema, on the other hand, are associated with more normal appearing bronchi. The extent of the atelectasis and the associated bronchial change varies considerably. In some animals it is very extensive, involving the greater portion of several lobes, while in other animals it involves only small areas in different lobes. In the killed animals that were well nourished and looked healthy, these changes are less marked or absent.

Microscopic Changes: In organs other than the lungs, microscopic changes are inconstant and of secondary importance. Metastatic abscesses have been found in the viscera. In the kidneys, especially, even in the gross, such abscesses are occasionally noticed. The splenic changes are those associated with chronic infection, and need not be discussed in detail. The lymph glands show a chronic lymphadenitis.

The changes in the *lungs* are the most interesting. In describing them, perhaps it would be best to begin with those lungs which show nothing markedly abnormal in the gross. Microscopically, there is a fairly marked emphysema. This is found associated with an organizing exudate in the bronchioles, or "bronchiolitis obliterans," as it may be called. This process evidently causes first a partial and later a complete occlusion of the bronchiole. The bronchiole may contain a small amount of purulent exudate, but the larger mass of exudate is organized and is composed of fibroblasts and blood vessels with some mononuclear cells (Fig. 19). The mass of organized exudate, forms a sort of mold of the bronchus, which is often covered with epithelium. It may extend well into the alveoli opening into the affected bronchiole (Fig 18). Not infrequently, the lung tissue surrounding such a bronchus shows an organizing pneumonia, with an active proliferation of

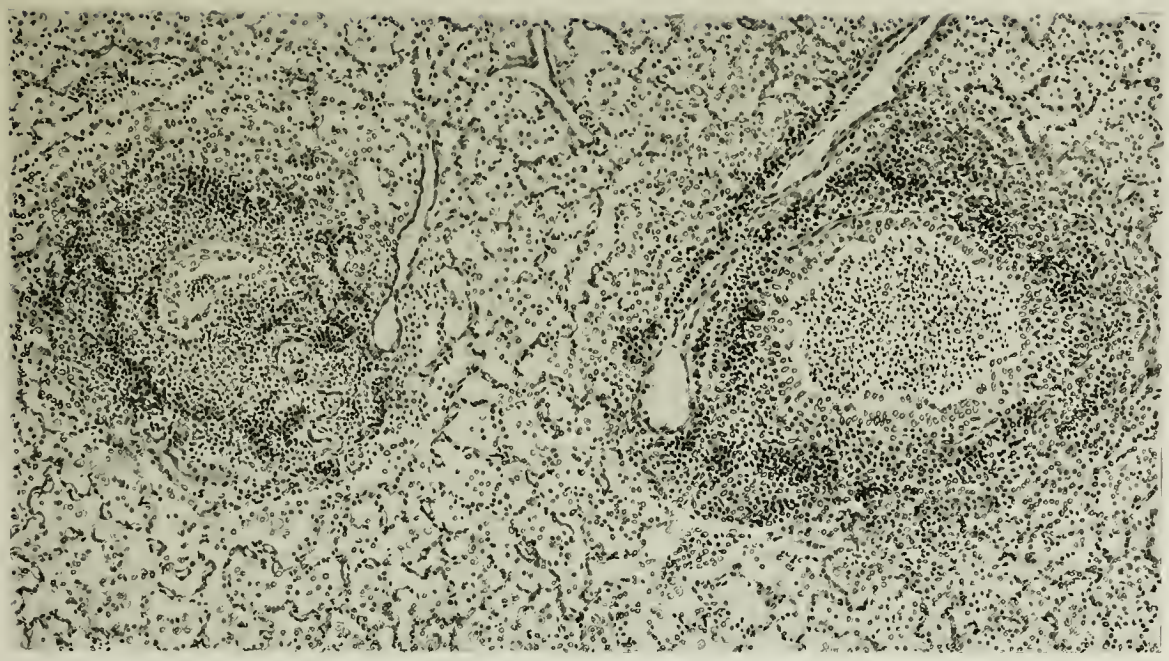


FIG. 17. PURULENT BRONCHITIS AND CHRONIC PERIBRONCHITIS IN A 23-DAY ANIMAL. IN THE BRONCHUS ON THE RIGHT THE MUCOSA IS INTACT IN MOST PLACES, BUT IN THE OTHER IT HAS BEEN LOST. THE CELLS IN THE LUMINA ARE CHIEFLY POLYNUCLEARS; THOSE IN THE OUTER COATS AND IN THE ADJACENT ALVEOLI ARE LARGELY MONONUCLEARS, WITH LYMPHOCYTES PREDOMINATING.

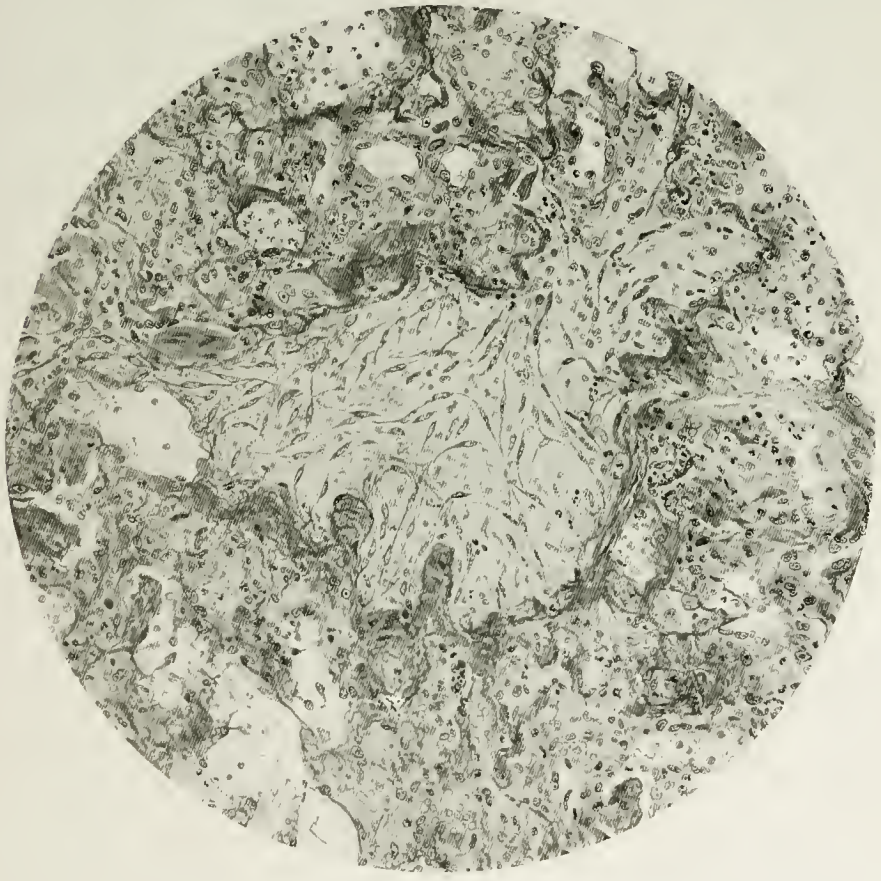


FIG. 18. ORGANIZING BRONCHIOLITIS, 5 DAYS AFTER GASSING. NOTE MASSES OF OLD FIBRIN IN BRONCHIOLAR AND ALVEOLAR WALLS AND LEUCOCYTIC REACTION EVERYWHERE.

fibroblasts and blood vessels extending from the septa into the alveolar exudate. In the more severe cases, the bronchi seem to be dilated, their lumina contain a muco-purulent mass, and the epithelial covering is thickened, being made up of several layers of cells; in other words, a bronchiectasis, as shown in Fig. 21. In some places the submucosa and other coats are extensively infiltrated with mononuclear wandering cells (Fig. 17).

Aside from the areas of organizing pneumonia which are found around the bronchi, the alveoli are, in many places, filled with a cellular exudate. This exudate is not composed of polynuclear leucocytes, or red cells, but almost entirely of large mononuclear cells with watery, vacuolated protoplasm, similar to the desquamated cells which are frequently found in the more chronic forms of pneumonia in man.

SUMMARY

By way of summary, it may be stated that the lesions found in this group of "chronic" gassed dogs are such as might have been expected from the findings in the acute and subacute stages. The sequence of events is fairly clear.

The infection, which starts very early after gassing, persists, and results in bronchitis, dilatation of the bronchi (bronchiectasis), organizing bronchitis, and, finally, a bronchiolitis obliterans. Along with the bronchial changes, there is often an organizing pneumonia. Emphysema and atelectasis, secondary to the bronchial lesions, occur with great regularity.

DISCUSSION

A number of questions arise in the study of the lesions found after gassing. For example, how is the initial intense edema of the lungs brought about? Does it precede or follow the death of the bronchial and respiratory epithelium? What is the cause of death in animals that succumb shortly after gassing before the development of pulmonary infection? Is the inflammatory reaction which begins in the lungs within a few hours due to the presence of pathogenic organisms or the direct result of a chemical injury?

Taking up the first question, it must be admitted that the exact mechanism by which the edema is produced is not clear. It has been assumed that the gas so injures the epithelium and the vessels beneath it as to render the latter permeable, thus allowing the fluid portion of the blood to escape. The escaped fluid constitutes, of course, the edema fluid. Other of the well-known theories as to the nature of edema might explain the phenomena here quite as well. It may be insisted that the edema develops before there is evidence of death of the respiratory epithelium, and that the former is a cause rather than an effect of the latter. In support of this idea, one may point to the large "blisters" in the trachea and bronchi already described, where it appears as though the epithelium had died after it had been lifted away from its nutrient base by the accumulation of fluid.

Another factor to be considered in this connection is the rôle which bacteria may play in the primary edema and in the subsequent changes that are found in the lung. These two points, namely, the effects of chlorine gas on the respiratory epithelium, and the rôle of bacteria in the changes following gassing, will be considered separately, with reports of experiments aimed at answering some of the questions just raised.

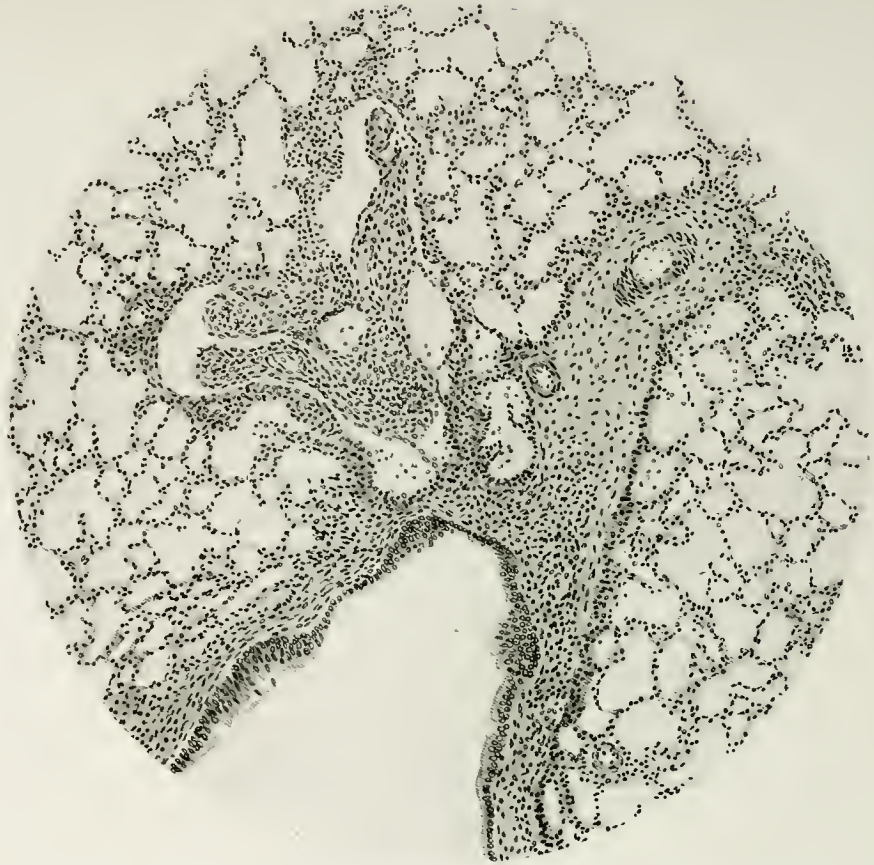


FIG. 19. OBLITERATING BRONCHIOLITIS. DOG KILLED 32 DAYS AFTER GASSING. THE LARGE BRONCHUS SEEN BELOW HAS A NORMAL (PROBABLY REGENERATED) MUCOSA. ITS MUSCULAR AND FIBROUS COATS ARE INFILTRATED BY MONONUCLEAR CELLS. THE SMALL TRIBUTARY BRONCHIOLE IS OCCLUDED BY AN ORGANIZED MASS OF TISSUE, WHICH IS ATTACHED TO THE BRONCHIOLAR WALL IN PLACES.

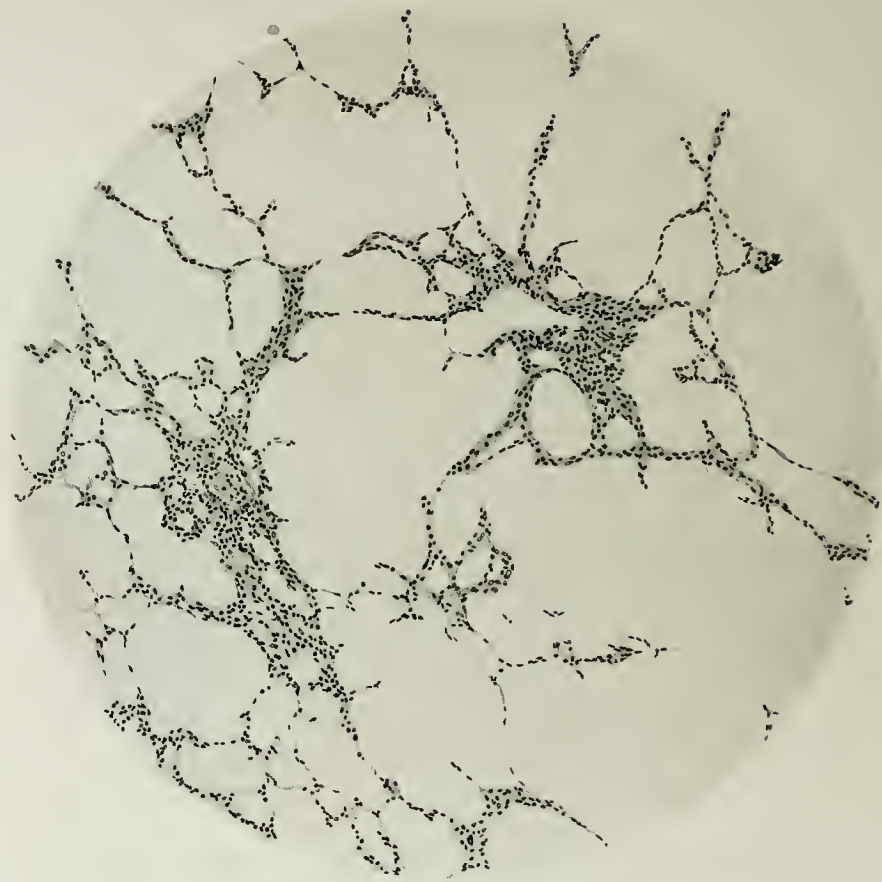


FIG. 20. SCARS AND EMPHYSEMA IN LUNG OF CHRONIC DOG. FIBROUS PATCH ON LEFT INCLUDES A SMALL BRONCHUS WHICH HAS BEEN ALMOST OBLITERATED BY AN ORGANIZING INFLAMMATION.

A. THE IMMEDIATE EFFECTS OF CHLORINE GAS UPON THE EPITHELIUM OF THE RESPIRATORY TRACT

With the ordinary histological methods, it is not possible to show that chlorine kills at once the epithelium of the bronchi or injures the alveoli in animals that succumb acutely to the gas.

As has been shown by Klotz, there is almost no histological change in the most acute deaths to indicate that the respiratory epithelium is killed. However, in the description of the findings in the early cases, in the first part of this paper, it was pointed out that in some instances, especially where the bronchioles are dilated, the alveolar walls are pink and free of nuclear staining. This suggests the possibility that if Schaefer's hypothesis be correct, chlorine in high concentration may cause a dilatation of the bronchioles and that when the gas reaches the alveoli, it may have a necrotizing action on the alveolar walls. Furthermore, it seems possible that the bronchiolar constriction, which is so very definite in many instances, may result from the chlorine gas acting in lesser concentration (Hill). By this constriction the alveolar epithelium and alveolar walls may be protected from the direct action of the gas.

VITAL STAINS

With ordinary histopathological methods it would be very difficult to come to any conclusions concerning the earliest changes in the epithelium, since considerable time necessarily elapses between the death of a cell and the katabolic changes which must take place before the histological picture of cell death results. There is, however, a means by which this can be approached. It is well known that vital stains, like trypan blue, when present in the circulation, stain many cells of the tissues. These cells never show nuclear staining. The dye appears as well-defined granules in the cell protoplasm. On the other hand, as soon as the cell is killed, the dye is immediately absorbed by cell and nucleus. We have here, therefore, a definite way of recognizing immediate cell death. In order to apply this test to our problem, several animals were given large quantities of trypan blue intravenously; and after they had become well saturated with the dye, they were exposed to chlorine gas. One animal died within 2 hours after gassing, and the other was killed after 24 hours. In both of these animals, the mucous membrane of the trachea and of the larger bronchi was intensely blue. Even the small bronchioles that could be seen on section of the lung had an intense indigo color. The tissue was fixed in formalin, and sections were made, cleared in glycerine, and studied immediately. These showed that all the epithelium of the respiratory tract as far as could be made out from the sections, had a distinct blue, nuclear stain (Fig. 22). In the larger bronchi, the nuclear stain alone could be made out in the mucous membrane. There was no coloration of the surrounding lung tissue. In the smaller bronchioles, however, it could be definitely seen that not only the epithelial lining of the bronchiole but also the alveolar walls in the neighborhood, stained blue. Nucleus and cytoplasm were involved alike in this process, and the picture conformed entirely to that seen in hematoxylin-eosin preparations, where foci of lung tissue stained diffuse pink (Fig. 12).

These experiments with vital stains allow the conclusion that chlorine gas kills the respiratory epithelium; and that when it reaches the smaller bronchioles, it destroys not only the epithelium but the alveolar wall as well. This dead tissue forms a splendid nidus for the development of bacteria and is unquestionably the site of abscesses found in animals that survive for a longer period.

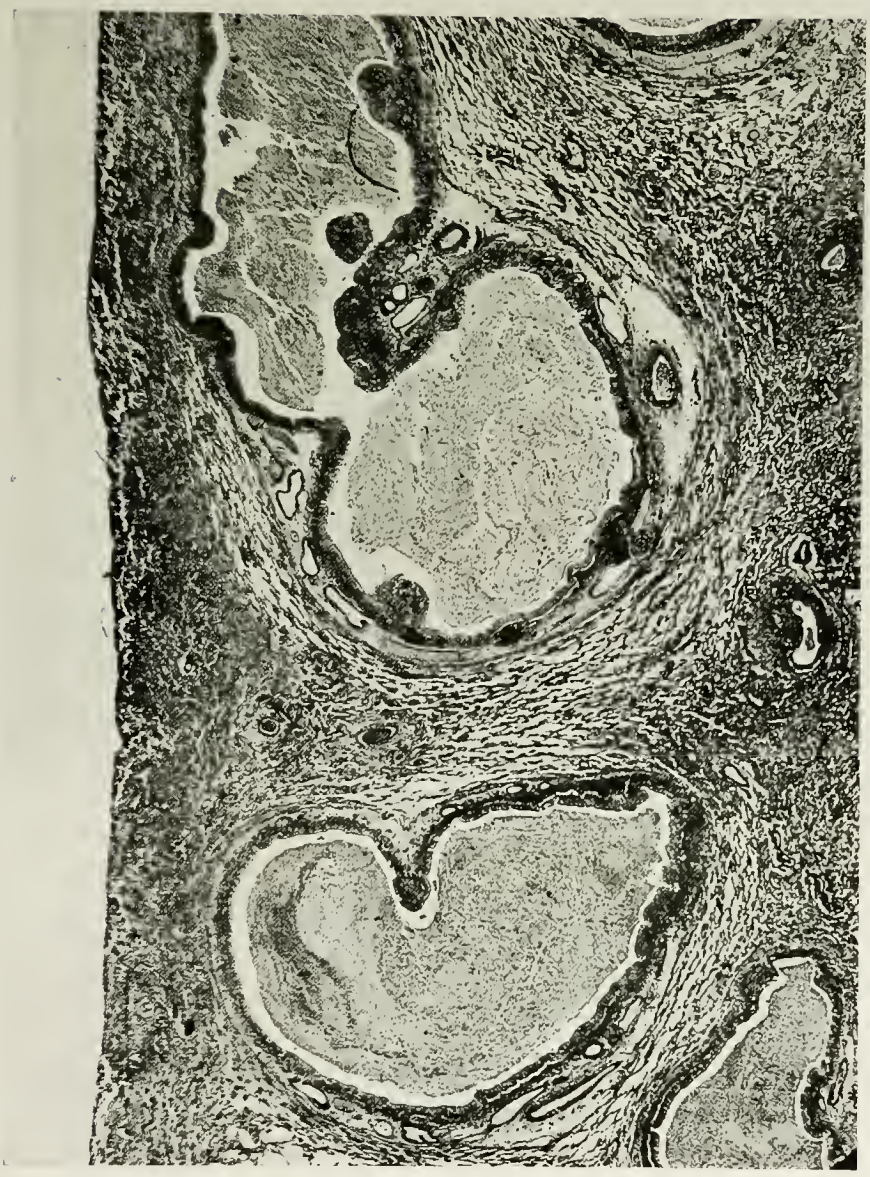


FIG. 21. BRONCHIECTATIC CAVITIES IN LUNG OF DOG DYING 39 DAYS AFTER GASSING. THERE IS COMPLETE ATELECTASIS OF PART OF LOBE SUPPLIED BY THESE BRONCHI.

B. THE CAUSE OF THE ACUTE INFLAMMATION OF THE RESPIRATORY TRACT AFTER EXPOSURE TO CHLORINE GAS

As has been indicated in the discussion of the above groups, histological manifestations of acute inflammation set in very rapidly after animals have been exposed to chlorine gas. They are present within two hours, and probably occur even earlier. This inflammatory process persists and is the cause of death in animals that survive the stage of acute edema. Furthermore, the inflammatory reaction is still evident in animals that have survived for a very long period, being found in dogs killed as long as six months after gassing.

Our attention was first called to the importance of bacteriological studies in this investigation by the finding of a pure culture of pneumococcus in the pus of the dilated bronchi of an animal that had survived for many days after exposure to gas. The experiments were taken up in the following order:

At first, cultures were made from the pneumonic lungs alone, but later a more systematic study was undertaken to determine the normal flora of the dog's mouth to ascertain whether this bore any relation to the organisms that were found in the pneumonic exudate, or in the more chronic lesions. These investigations are not yet entirely completed, but sufficient evidence is at hand to permit the following statements:

In the first series, the lungs from 25 animals were cultured. This includes dogs that survived exposure to chlorine gas from 12 hours to 48 days. The findings are so uniform that it is unnecessary to group the cases. Suffice it to say that in six no growth was obtained; in one a pure culture of a small Gram-negative hemoglobinophilic bacillus was recovered. In twelve, a pure culture of pneumococcus resulted, and in six, the pneumococcus plus the small bacillus were both obtained in pure cultures. In five of these animals, blood cultures were also made. Two of these animals succumbed after 24 hours, one after three days, one after six, and one after thirty-eight days. In all of these, pure cultures of a Gram-positive diplococcus similar to the pneumococcus and similar to the coccus obtained from the lung culture were found.

A more detailed study was then obtained on a series of twenty-one dogs. The normal flora of the mouth was first determined. The cultures were made from the mouth on two successive days, and the dogs were then gassed. Cultures were taken from the blood and lungs at autopsy of dogs dying within a period of three days after gassing. The findings are of interest. In addition to common organisms, such as the streptococcus, staphylococcus, *Bacillus subtilis*, etc., there were found in the mouth of each of the dogs before gassing two organisms: a Gram-positive diplococcus that agglutinated with pneumococcus Group II serum at a dilution of 1:2, and a small Gram-negative hemoglobinophilic bacillus, very similar to the influenza bacillus. In fourteen cases, both of these organisms were found in the mouth; in six, the pneumococcus alone was found; and in one, the Gram-negative bacillus alone was obtained.

The lung cultures at the death of the animals were negative in four cases. (In all of these animals, death resulted very soon after exposure.) In nine, the pneumococcus alone was obtained. In four, both the pneumococcus and the Gram-negative bacillus were recovered, and in four, the Gram-negative bacillus alone was recovered.

Blood cultures were made on all of these cases. In only five, were they positive; and in all, the pneumococcus alone was recovered.

The *conclusion* from this study is that organisms that normally inhabit the mouth of

PLATE IV

FIG. 22: FROZEN SECTION OF LUNG OF DOG VITALLY STAINED WITH TRYPAN BLUE BEFORE GASSING AND KILLED IMMEDIATELY AFTER GASSING.

THERE IS A DIFFUSE STAINING OF THE CELLS LINING TRACHEA AND BRONCHI, AND ALSO OF THE ALVEOLAR WALLS IN PLACES. SHOWING THAT THESE CELLS ARE DEAD.

the dog find their way into the bronchi and lungs of the dog shortly after gassing and remain there for a long time in animals that survive the acute period.

CONCLUSIONS

(*1*) Chlorine gas causes immediate death of the epithelium lining the upper respiratory tract. This is proved by the use of vital stains, by means of which a staining reaction, characteristic of dead cells, can be demonstrated immediately after gassing, before it is possible to recognize a fatal cell injury by ordinary staining methods. Areas of focal necrosis in the lung itself are also to be attributed to the direct action of the chlorine on parts of the lung not protected by bronchiolar spasm.

(2) The destruction of the epithelium of the trachea and bronchi removes the normal protective mechanism of the upper respiratory tract and allows pathogenic bacteria from the mouth to find their way into the injured bronchioles within a very short period after the epithelium has been destroyed. Bacteriological investigations, which show that the pneumococcus and a small Gram-negative hemoglobinophilic organism, normal inhabitants of the dog's mouth, can be cultivated from the lung as early as one-half hour and as late as four days after gassing, give support to the view that the lungs' normal barrier against infection is lost.

(3) The bacterial infection results in a pneumonia—lobar, lobular, or necrotizing. The pneumonia is associated in all cases with an infection of the bronchi. The infection tends to persist in animals surviving the acute period, and results in a chronic bronchitis, bronchiolectasis, or obliterating bronchiolitis, with scarring of the lung. These lesions are demonstrable in dogs dying or killed as late as six months after gassing.

(4) The irritating action of chlorine results in a bronchiolar spasm, which, interrupting the normal inflow and outflow of air, causes an acute emphysema or atelectasis, most marked in animals dying in the acute stage.

(5) Edema of the lungs, trachea, and bronchi is probably the most striking feature of the acute death from chlorine gassing. It is probably brought about by the direct action of the gas, which so damages the lining epithelium and the vessels beneath as to allow the escape of fluid through the vessel walls. The coagulation of the plasma as it passes out through the alveolar wall results in a deposition of fibrin in this situation, which seriously impedes the flow of blood through the lungs.

(6) Edema of the lungs after gassing constitutes only one of the phenomena of the gas injury to be combated. The bacterial infection, which regularly supervenes in animals surviving more than a few hours, is a condition of equal if not greater importance.

TABLE I

	Dogs dying	Autopsied: Died	Autopsied: Killed	Autopsied: Total	Examined Microscopically: Died	Examined Microscopically: Killed	Examined Microscopically: Total
Group I.	First 12 hrs.	62	3	65	50	3	53
	12 to 24 hrs.	110		110	72		72
Group II.	2nd day	25		25	14		14
	3rd day	8		8	6		6
	4th day	13		13	11		11
Group III.	5th day	7		7	5		5
	6th day	4		4	3		3
	7th day	4		4	3		3
	8th day	2		2	2		2
	9th day	3		3	0		0
	10th day	2		2	0		0
	11th day	2		2	2		2
	12th day	1		1	0		0
	14th day	1		1	1		1
Group IV.	15th to 30th day	11	8	19	7	5	12
	30th to 193rd day	15	45	60	11	36	47
	Total	270	56	326	187	44	231

TABLE II

	Per Cent Showing Pneumonia: All types	Early	Advanced	Organizing	Per Cent Showing Bronchitis & Bronchiolitis: All types	Early	Advanced	Organizing, or obliterative
Dogs dying first 12 hrs.	18	18			36	36		
" " 12–24 hrs.	54	26	28		56	27	29	
" " 2–4 days	95	26	65	4	61	13	48	
" " 5–14 days	100		11	89	69		50	19
" " 15–30 days	83	8	23	52			17	8
" " 31–193 days	24		7	17	10			10
Dogs killed 15–193 days	24		7	17	51		17	34

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THE PATHOLOGY OF PHOSGENE POISONING

BY

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THE PATHOLOGY OF PHOSGENE POISONING

INTRODUCTION

Phosgene ($COCl_2$) was first prepared by John Davy in 1812 by exposing a mixture of equal parts of carbon monoxide and chlorine to sunlight. The name phosgene was given the gas to suggest the part played by light in its formation.

Up to three years ago, phosgene had its chief use in the manufacture of aniline dyes and certain pharmaceutical preparations, such as creosotal, hedonal, aristochin, etc. In 1915, the toxic properties of the gas were first turned to account by the Germans, who began using it on the Western front some time in December of that year. Its use in gas warfare has rapidly increased in the last two years, as this form of fighting has developed. It has been utilized not only in gas cloud attacks, less popular now than before adequate protective measures had been devised, but also in gas shells. Owing partly to its relatively high boiling point, 8° C., and its poor diffusibility, phosgene is practically never used alone, but is mixed with one or more of the other more diffusible gases. In gas clouds, it is often combined with chlorine; in shells, a much used combination is phosgene, diphosgene (trichloromethylchloroformate, $C_2O_2Cl_4$) and diphenylchlorarsine ("sneezing gas").

Though much less irritating to the nose and eyes than chlorine and less likely to cause immediate asphyxiation, phosgene has, nevertheless, come to be regarded as the more effective fighting weapon, producing a larger number of casualties, with a high per cent. of fatalities.

Phosgene owes its toxicity to the property of being readily split up in the presence of water into HCl and CO_2. When breathed, little decomposition takes place until the gas reaches the lungs, where in the smaller bronchi and in the alveoli, it comes into contact with sufficient water vapor to bring about the evolution of HCl. According to Hoover, much of the phosgene taken into the lungs is probably absorbed as such, decomposition taking place gradually in the tissues. This would explain the severe damage found in the bronchioles and the alveoli and would account for the slower and more gradual development of the signs of pulmonary injury than is the case with certain other gases of the pulmonary irritant group, such as chlorine, or bromcyanogen, which do not require for their action any preliminary decomposition. It may be observed in this connection that although the phosgene injury is apparently referable to the HCl formed from it, the effects of phosgene and HCl inhalations are by no means identical. On the contrary, the lesions produced by the two gases differ both in kind and in degree. HCl strikes first and hardest the larynx and trachea, damaging less the distal portion of the respiratory tract, that is, the bronchioles and pulmonary alveoli; while in the case of phosgene poisoning, it is the distal part which suffers most. The importance of the locus of decomposition is further emphasized by the observation that if animals are exposed to HCl and phosgene in equivalent concentrations,

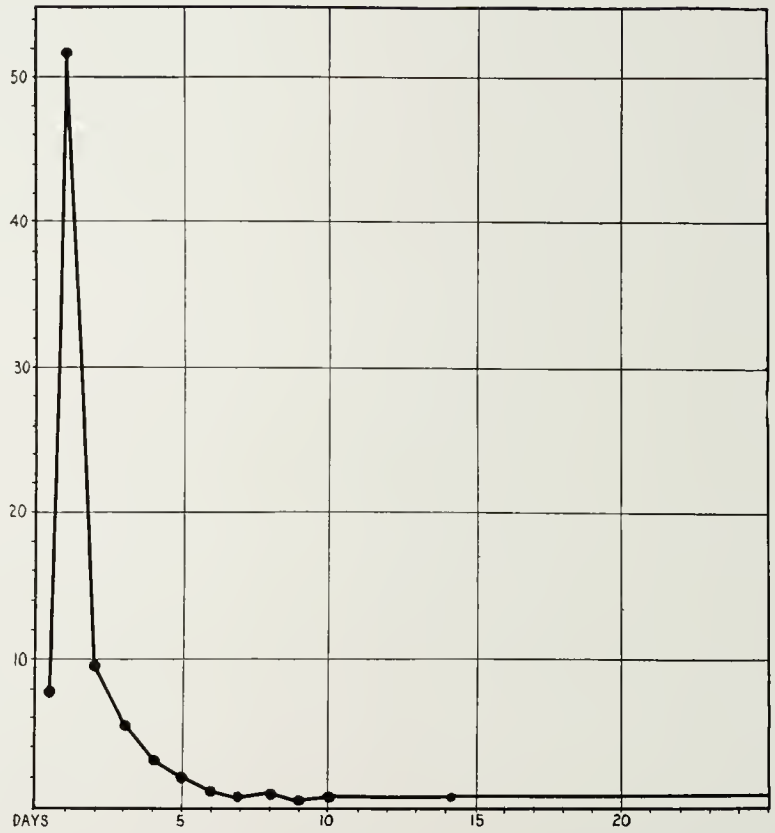

CHART I. HIGHEST POINT OF CURVE IS REACHED BETWEEN 12 AND 24 HOURS AFTER GASSING. DAILY NUMBER OF DEATHS AFTER THE 4TH DAY IS SMALL.

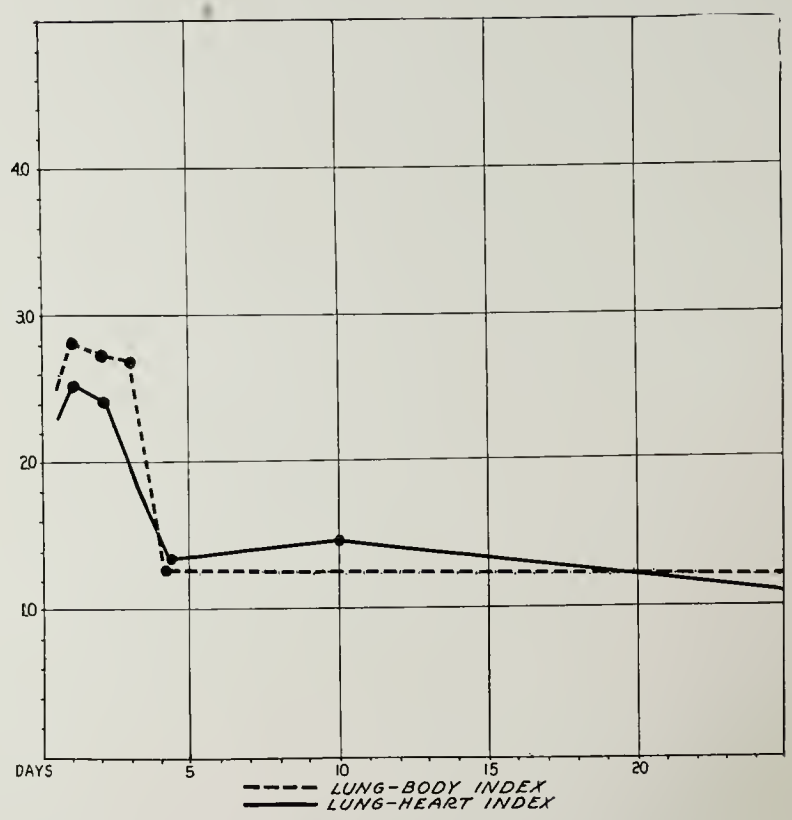

CHART II. CURVES SHOWING DEGREE OF EDEMA AT DIFFERENT PERIODS AFTER GASSING, BASED ON PROPORTIONATE WEIGHTS OF LUNGS. HEART AND BODY. IT IS SEEN THAT THE LUNG-HEART AND LUNG-BODY CURVES RUN PARALLEL, ALTHOUGH THE FORMER GIVES HIGHER READINGS IN THE ACUTE PERIOD. BOTH APPROACH THE NORMAL ABOUT THE 5TH DAY, BUT THE BASE LINE IS NOT REACHED EVEN AFTER 20 DAYS. ONLY "KILLED" ANIMALS WERE USED IN COMPUTING THE FIGURES FOR THE 3D TO THE 30TH DAYS.

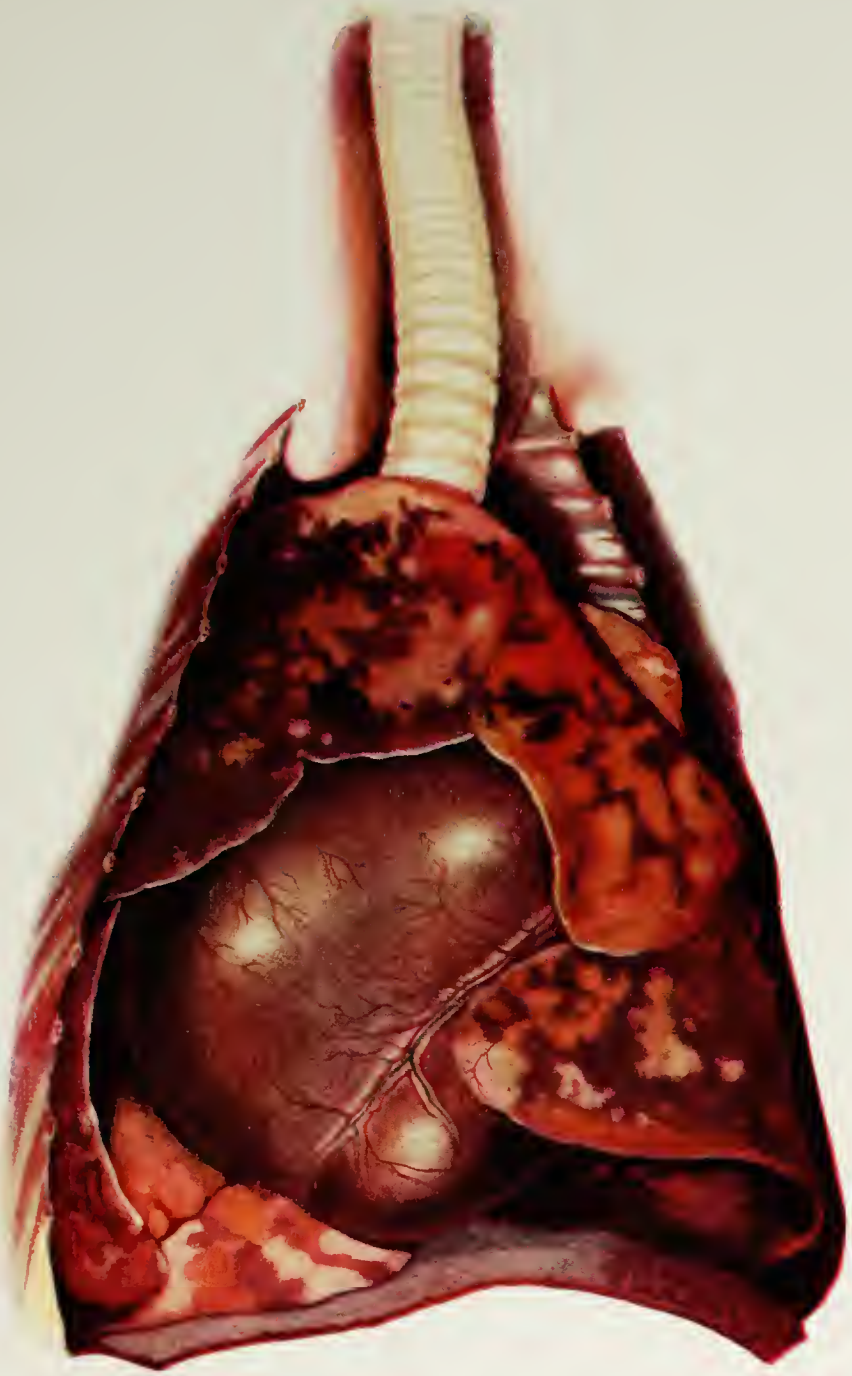

PLATE V

FIG. 1: HEART AND LUNG OF DOG DYING 24 HOURS AFTER GASSING. LIGHT PATCHES OF ACUTE EMPHYSEMA ALTERNATE WITH DEEP RED CONGESTED AND PARTIALLY COLLAPSED AREAS. LUNGS ARE VOLUMINOUS; HEART IS DILATED, EXPECIALLY RIGHT SIDE.

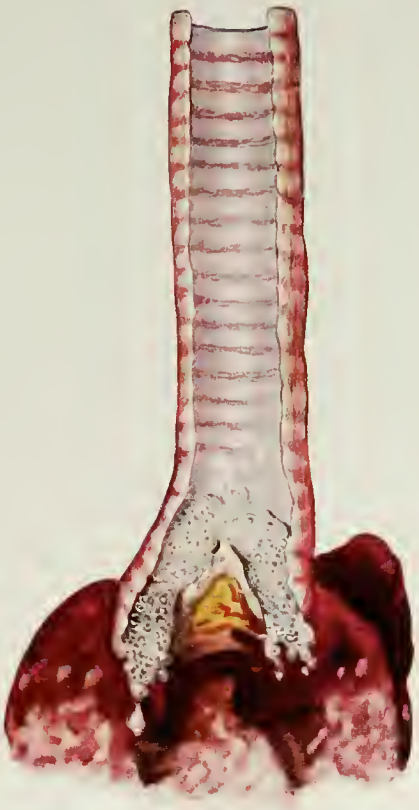

PLATE VI

FIG. 2: TRACHEA OF SAME CASE, OPENED FROM BEHIND. FROTHY FLUID POURS OUT OF BOTH BRONCHI. TRACHEAL MUCOSA IS NORMAL SAVE FOR SLIGHT CONGESTION OF VESSELS IN THE INTERCARTILAGINOUS ZONE.

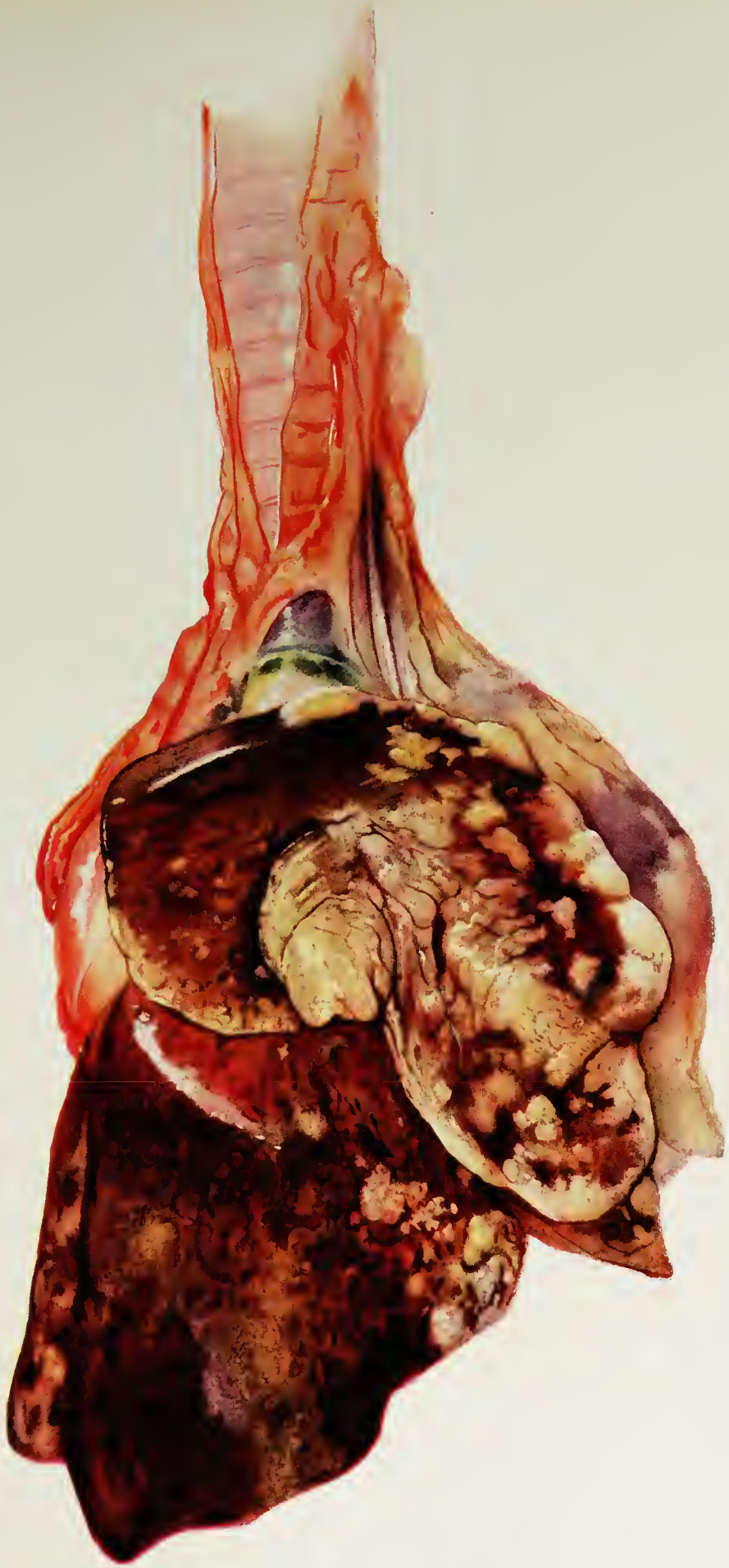

PLATE VII

FIG. 3: LUNGS OF DOG EXPOSED TO PHOSGENE. (CONC. 0.27 FOR 30 MIN.) KILLED AFTER 12 HOURS.

HCl is found to be less toxic, probably because its action is expended on the less vital proximal portion of the respiratory tract.

The effects on man of the various noxious gases used in modern warfare have been described in a general way in numerous reports by British, French, Italian, and American Medical Officers. In very few of the published papers, however, does one find discussed the effects of the individual gases of the respiratory irritant group. Phosgene and chlorine, which are, perhaps, the most important members of this group, show very definite points of difference in their action on animals; but since in warfare a mixture of the two gases is often used, it is not surprising to find little said in reports from the battle field of the differential diagnosis and comparative pathology.

There is, however, a very good discussion of the clinical aspects and pathological physiology of phosgene poisoning by Hoover, who made a study of several hundred cases at a Casualty Clearing Station near the battle front, where patients arrived a few hours after gassing. We have been unable to find in the accessible literature any other clinical reports dealing specifically with gassing by phosgene.

In the present report we shall take up only the pathology of phosgene poisoning produced experimentally in dogs. So far as has been determined, the effects of the gas on animals differ in no essential way from those seen in man; and since it is possible in animals to observe the changes produced from the very earliest stages to the latest, the advantages of the experimental method for working out the detailed pathology of the gas injury and the relation of this to the clinical features of the gassed state, are obvious. Animal studies are particularly valuable in throwing light upon the late effects of gassing, which, on account of the number of gassed soldiers who become chronically disabled, have aroused considerable interest.

MATERIAL FORMING BASIS OF REPORT

The material on which this report is based consists of dogs gassed in the Department of Physiological Chemistry of Yale University and utilized by F. P. Underhill and his coworkers for determining the toxicity of phosgene in varying concentrations and for carrying out various physiological studies leading to a method of treatment.

The dogs were exposed in closed chambers for 30 minutes to phosgene in concentrations varying from 44 to 120 parts per million. It may be well to state here that although with higher concentrations there is, as Underhill has shown, a more rapid onset of symptoms and a larger per cent. of fatalities, the pathological changes in the respiratory system, as far as we have been able to determine, are practically the same with all of the concentrations used, except in the time required for the development of the lesions.

Animals dying after gassing were turned over to us immediately for autopsy, and many of the recovered dogs, that is, those which did not succumb within a few days, were placed at our disposal. The latter were sent to a farm, where a certain number died, sooner or later (see Table I, Group III). The remainder were killed at intervals up to 129 days after gassing. Post-mortem examinations were made and records of gross findings kept in all cases. In a large number of selected cases, the tissues were examined microscopically.

A review of the gross and microscopic findings in this large series of animals representing all stages of the gas injury up to four months after gassing, will indicate, in our opinion, the nature and sequence of the lesions in man, and may throw light particularly on the late effects of gas poisoning, hitherto little studied pathologically.

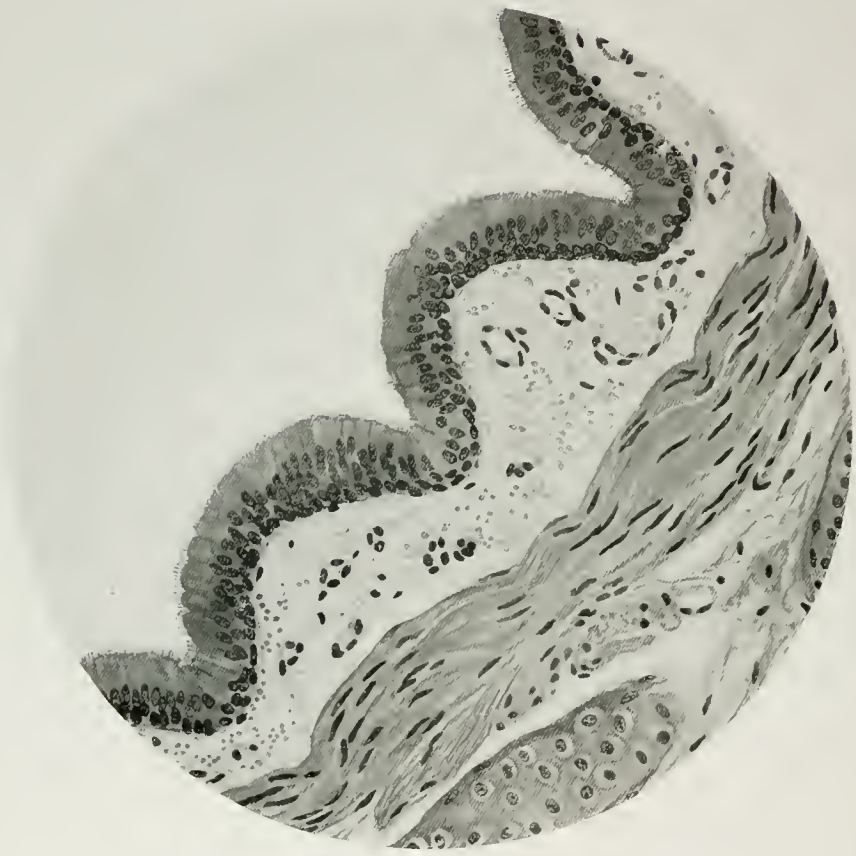

FIG. 4. WALL OF LARGE BRONCHUS SHOWING UNINJURED MUCOSA IN ANIMAL DYING 24 HOURS AFTER GASSING.

As might be expected, the changes found at the autopsy after gassing vary greatly with the length of time the animal has survived. For this reason it will make description easier if the animals dying in the several stages, which may be conveniently termed acute, subacute, and chronic are taken up separately.

On this basis three groups have been made.

GROUP I. *Animals Dying or Killed Within 48 Hours After Gassing.* (*Acute Period.*)
GROUP II. *Animals Dying or Killed 3 to 10 Days After Gassing.* (*Subacute Period.*)
GROUP III. *Animals Dying or Killed 11 to 129 Days After Gassing.* (*Chronic Period.*)

The *accompanying tables* show the number of animals falling into each of these groups, and, in addition, the deaths by days up to the 15th day. It is at once evident that, omitting the killed animals, the majority of the dogs autopsied died in the first 24 hours, and that the number belonging to each succeeding 24-hour period diminishes progressively and rapidly to about the 5th day when the base line is nearly reached (see curve, Chart I). It should be made clear, however, that the figures given here and the curve based on them, refer only to *autopsied* animals and do not include all gassed animals from any single experiment or series of experiments, and, therefore, are not intended to show, except in a rough way, the time at which death is likely to occur after phosgene gassing under similar conditions as to time of exposure and concentration of gas. Accurate figures and curves bearing on this point will appear in the reports by Underhill and his co-workers.

GROUP I. *Animals Dying or Killed Within 48 Hours After Gassing.* (*Acute Period.*)

There were autopsies on 260 dogs belonging to this group. If we exclude the *killed* animals, we find that in 68 per cent. of the entire series of animals death occurred in the first two days. Analyzing the figures further, it is seen that most of the deaths in this period took place between 12 and 24 hours after gassing, there being relatively few in the first 12 hours and not many more between 24 and 48 hours. However, it has been shown by Underhill and others that exposure to very high concentrations of gas increases the number of deaths in the first 12 hours and that lower concentrations give a larger proportion of deaths on the second day.

Autopsy Findings.

The *gross anatomical changes* in animals dying in this early period, though very striking, show little variation. The first two or three autopsies are startling, by reason of the brilliancy and unusualness of the lesions in the respiratory system. The next half dozen or so hold one's interest, but do not thrill. After that a feeling of monotony is likely to develop in the pathologist, especially if the autopsies follow close upon one another.

Body: Frothy fluid sometimes clear, sometimes blood-tinged, oozes from the mouth; the eyes may be a little reddened, but a well-marked conjunctivitis is exceptional. Post-mortem changes develop rapidly as in chlorine poisoning and are conspicuous if the autopsy is delayed for more than 3 or 4 hours, with the body at room temperature.

The body is generally well nourished, only animals in good condition being selected for gassing, but the body weight is regularly less than at the time of gassing. This reduction is often considerable, as much as 1.5 kilos in large dogs. It is probably due, in large part at least, to the loss of fluid by mouth.

Abdomen: The engorgement of the great vessels and the congestion of the viscera are

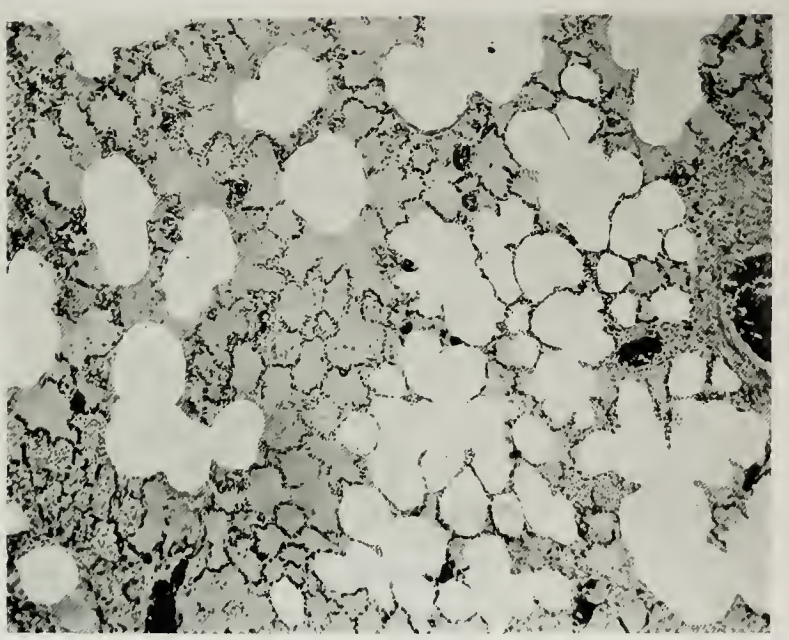

FIG. 5. EDEMA AND ACUTE EMPHYSEMA IN ACUTE STAGE. EDEMATOUS FLUID, OWING TO ITS RICHNESS IN ALBUMEN, APPEARS AS A HOMOGENEOUS MASS RESEMBLING THE COLLOID MATERIAL OF THE THYROID GLANDS.

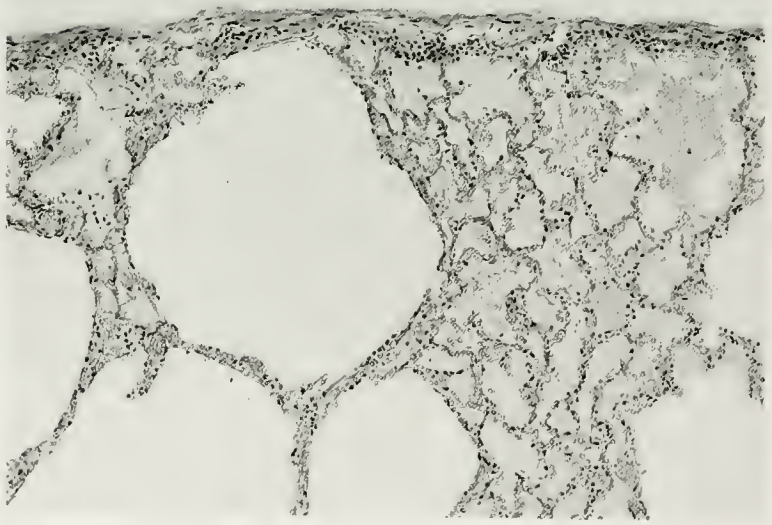

FIG. 7. HIGHER MAGNIFICATION OF AREA IN SECTION ILLUSTRATED BY FIG. 6. EDEMA IS MORE EVIDENT.

quite striking and constitute the only positive findings in the abdomen. The *liver* is enlarged and extends far below the costal margin. It has a dark purplish color, which it loses in part as the vessels are cut, allowing the blood to drain out. The *spleen* is only slightly enlarged, but like the liver and other abdominal organs, has the general appearance of acute congestion.

Thorax: As the sternum is removed, the great volume and non-collapsibility of the lungs are at once evident. The anterior margins nearly meet in the median line and tend to overlie the heart, and the pleural spaces are obliterated. The loose tissue of the anterior mediastinum is somewhat edematous, but an excess of fluid in either the pleural or pericardial cavities is unusual.

The *heart* is, as a rule, considerably enlarged (dilated), and the enlargement though more marked on the right side, involves also the left (Fig. 1). In one animal that succumbed seven hours after exposure and was autopsied immediately, the apex of the heart was bifid as the result of the excessive dilatation of the right ventricle. The cavities and valves present nothing abnormal, except for the presence of flame-like hemorrhages beneath the endocardium, which are encountered not infrequently. We found them in approximately 15 per cent. of the cases. The commonest location of the hemorrhages is in the region of the papillary muscles of the left ventricle.

Respiratory Tract: In all instances, the neck organs,—tongue, larynx, trachea, esophagus,—were taken out with the lungs and examined in the order followed in the description.

The *larynx* may be slightly edematous but is otherwise normal. The *trachea* is filled more or less completely with frothy fluid such as was seen oozing from the mouth (Fig. 2). In the *bronchi*, which are always well filled, there is more fluid than froth. The fluid is clear, faint yellow, and looks like serum. In the smaller bronchi, it may be slightly viscid or even tenacious owing to an admixture of mucus and fibrin.

The mucosa of the trachea and of the larger bronchi is smooth. That covering the cartilaginous rings is pale, while that of the intervening zone is slightly reddened from the injection of its vessels (Fig. 2). On close inspection, these appear as a fine network, but are not much more prominent than normally. Toward the smaller bronchi, the congestion is more definite but is nowhere conspicuous.

The *lungs* are very voluminous and heavy. The pleura is smooth, glistening and moist, and its lymphatics are often conspicuously dilated. An acute pleurisy at this early period has not been seen.

The color of the lungs is most striking. They are extraordinarily mottled, large whitish patches alternating with deep red ones (Fig. 1). Over the whole, there is often a bluish hue corresponding to the ashy cyanosis seen clinically in man. The light-colored patches are more or less elevated and very crepitant and are easily recognized as areas of acute emphysema. The individual distended alveoli can be made out with the naked eye, and are particularly clear with a low-power magnifying glass. The darker parts of the lungs appear by contrast to be collapsed, but this is obviously only partially the case, since the lung is voluminous throughout. The dark color is due to an extreme congestion of the vessels. The relative amounts of the light emphysematous lung tissue and the dark congested partially collapsed portions vary considerably. In some cases almost the entire lung is dark, bluish red, with only a few scattered emphysematous patches in the upper lobes (Fig. 3). In other instances, where the duration of life after gassing is the same, a widespread emphysema with little of the dark red tissue is found. In general, the lower lobes are darker, the emphysema being more pronounced in the upper and middle portions.

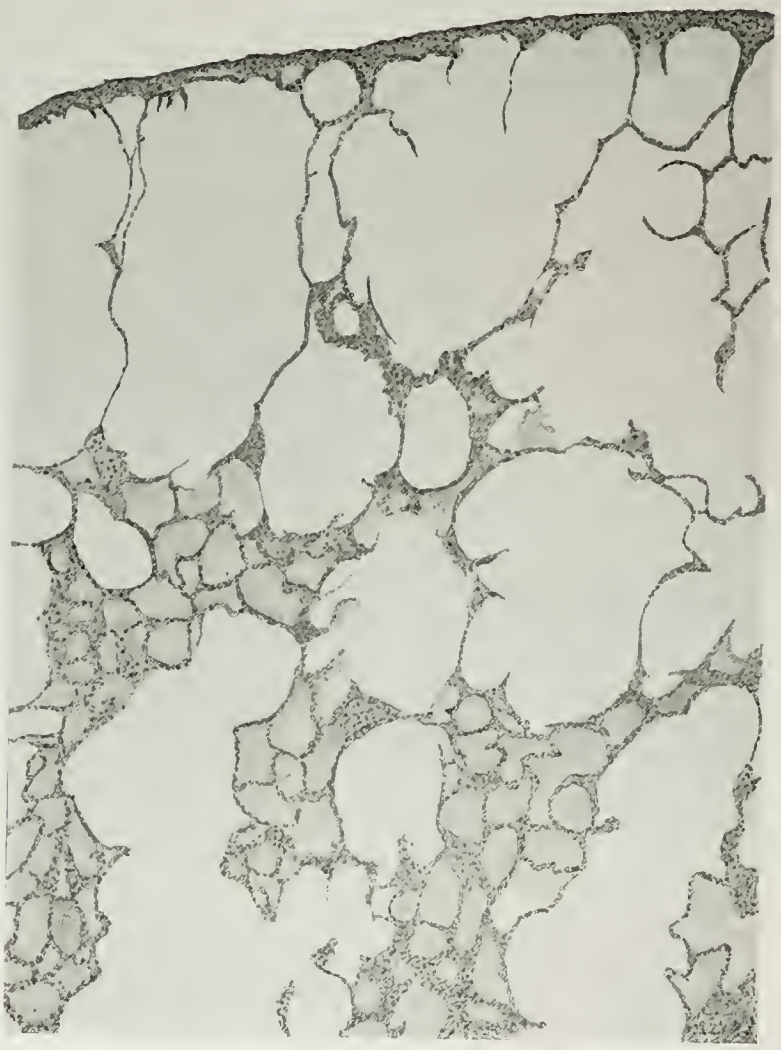

FIG. 6. ALTERNATING PATCHES OF ACUTE EMPHYSEMA AND ATELECTASIS IN LUNG OF DOG DYING 12 HOURS AFTER GASSING. THERE IS CONSIDERABLE EDEMA IN THE COLLAPSED AREAS.

On palpation the lung is doughy and pits on pressure, with an expression of fluid through the bronchi. In animals dying in the first 12 hours, this edematous condition is not as marked, while in those passing the 24-hour period, it may become the most prominent feature, quite overshadowing the congestion and emphysema. In such cases the rounded margins are quite translucent, and the dark, bluish red color of the earlier period is turned into a watery pink, as though even the stagnant blood in the vessels were diluted.

On cutting into the lung, fluid oozes from the surface and a great quantity can be expressed. From the very pale translucent areas, the fluid is straw-colored, while in the dark areas, it is red from admixed blood.

In estimating the extent of the edema, the weight of the lungs may be taken as a fair index, although it is evident that the greatly increased weight of the organ is due not to the edema alone but also to the extreme congestion, regularly present. Indeed, in the first few hours before the edema becomes well developed, the congestion is clearly responsible for the larger share of the increased weight.

In order to get a reasonably correct estimate of the degree of edema and congestion on the basis of lung weights, we have adopted indices based on the heart-lung and body-lung ratios. The former was suggested by Barcroft and has been used by English observers. The normal ratios were determined from autopsies on 15 normal dogs; lung-heart, 1.30; lung-body, .0115.

Dividing the ratio obtained in the gassed animals by the normal ratio, a figure is obtained which probably represents fairly accurately the degree of edema and congestion present. Of the two indices, we regard that based on the lung-body proportion as the more accurate in the average, medium-weight, well-nourished dog, but it often gives in small or very thin animals readings that are obviously too high. The objection to the lung-heart proportion is that even slight variations in the method of trimming the heart result in large errors.

Using the two methods, we have found that the lung increases rapidly in weight, reaching a maximum 18 to 24 hours after gassing when it may be, in fatal cases, more than four times the normal. For exact figures and further data on this point, see Table II and Chart II.

The cut surface of the lung is generally uniformly smooth and moist, but close inspection may reveal a number of tiny grayish foci scattered everywhere, but most numerously in the lower lobes. These are patches of early broncho-pneumonia. They are often overlooked in the gross specimen on account of the massive edema and congestion present, which obscure the picture. The smaller bronchi are somewhat more conspicuous than normally owing to the edema of their walls.

The *blood vessels* are normal. No thrombi have been found in veins or arteries.

The *bronchial lymph nodes* appear somewhat enlarged, and on section are edematous.

The organs not mentioned thus far, esophagus, stomach, intestines, pancreas, adrenals, thyroid, brain, may be dismissed in few words. The *esophagus* shows nothing pathological. In the *stomach* and *intestines*, congested areas and hemorrhagic erosions are occasionally found, but since we have seen the same picture quite as often in non-gassed animals, we are inclined to think the changes are in no way related to the gassing.

In 15 cases, the *brain* was examined, but in none could we demonstrate capillary hemorrhages or inflammatory lesions, such as have been described by Mott in gassed soldiers.

The *pancreas*, *adrenals*, and *thyroid* show no gross abnormality.

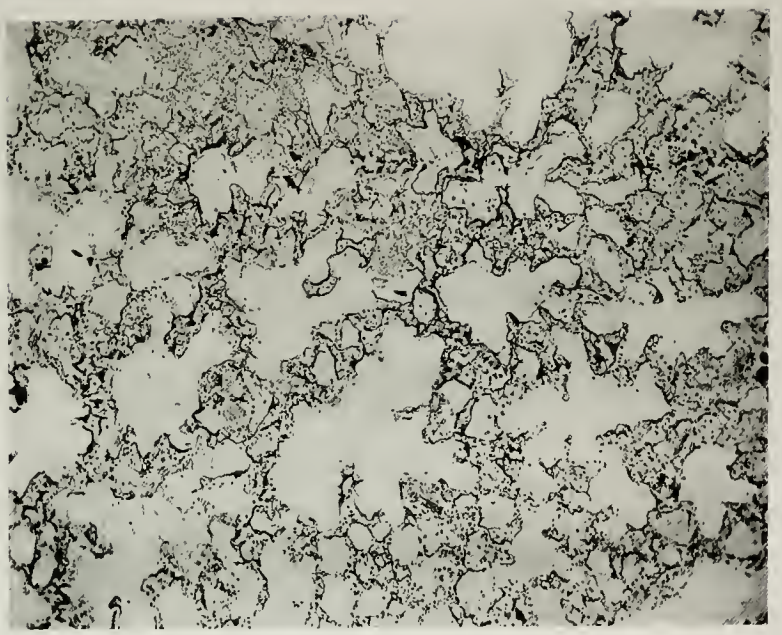

FIG. 8. LOW POWER PHOTO-MICROGRAPH OF SECTION OF LUNG FROM A 2-DAY DOG STAINED FOR FIBRIN. ALVEOLI ARE OUTLINED BY THE HEAVY DEPOSIT OF FIBRIN WHICH COVERS AND INFILTRATES THE SEPTA EVERYWHERE.

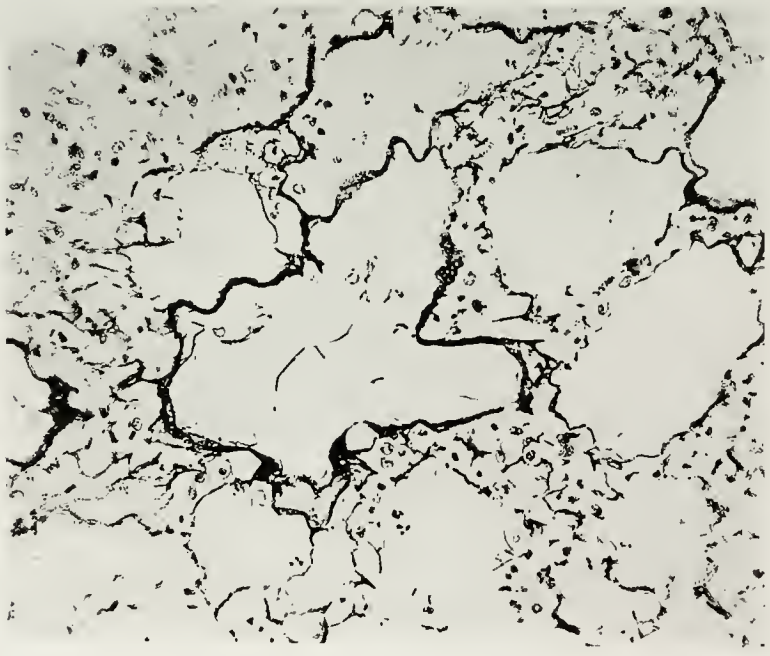

FIG. 9. HIGHER MAGNIFICATION OF FIELD IN FIG. 8. THE INFILTRATION OF THE ALVEOLAR WALLS WITH FIBRIN IS CLEARLY SHOWN. IN THE ALVEOLAR SPACES THERE IS AN INFLAMMATORY EXUDATE OF POLYNUCLEAR LEUCOCYTES, FIBRIN AND MONONUCLEAR CELLS.

Microscopic Findings.

Microscopically, the changes of most interest and importance are found in the *lungs.* The alveoli vary markedly in size. In some places they are exceedingly large with very thin walls in which blood vessels are made out with difficulty, while near by one sees areas where the alveoli are small, with thick walls in which the vessels stand out prominently as tortuous tubes distended with blood (Figs. 6 and 7). The alveolar walls, in general, appear naked; that is, there is considerable desquamation of the alveolar epithelium, so that the conspicuous wall of the alveolus looks almost like a greatly dilated capillary. This is most evident in the collapsed patches. The alveoli nearly everywhere contain more or less of the edematous fluid (serum), which may appear either as a homogeneous, pink-staining material resembling thyroid colloid (Fig 5), or as a faint, granular precipitate (Fig. 7), the appearance depending not only on the actual quantity of fluid present but on its content of albumin, a higher content giving a denser precipitate with the fixative.

In addition to serum, there is generally some fibrin in the alveoli; occasionally, this is abundant. But it is in the alveolar walls that fibrin appears in greatest amount, and where in our opinion its presence has most significance. With special stains, a thick layer lining the alveolus can be demonstrated in many places, with frequent strands crossing the capillary to a similar layer on the wall of the adjacent alveolus (Figs. 8 and 9). The presence of fibrin in this situation must not only interfere with gaseous exchange but also constitute a serious obstacle to the flow of blood through the lungs. An anatomical basis for the dilatation of the right side of the heart, so regularly observed, is thus found.

Although the relation is not absolutely clear, variations in the size of the alveoli are unquestionably associated with changes in the patency of the bronchi, particularly the smaller. What these changes are may be stated briefly.

The very large *bronchi*, like the trachea, show little change, though there may be an excess of mucus and some polynuclear leucocytes in their lumina. But as soon as we reach that portion of the bronchiolar tree, not protected by cartilaginous rings, distortions are found. In many instances the walls seem to be so firmly contracted that the lumen of the bronchus is obliterated. The bronchiolar musculature is prominent.

This contraction, which is sometimes very irregular and corkscrew-like, may extend into the finer bronchioles, but is usually not prominent in the smaller ones near the atria of the alveoli. In fact, these smallest tubes are frequently greatly dilated and appear as large sausage-shaped sacs, which communicate freely with groups of dilated alveoli. In other instances the bronchioles may be partially obstructed with a dense plug of inflammatory exudate and necrotic cells (Fig. 10).

While it is difficult to work out the exact relationship of these changes in the bronchial tree to the changes in the lung itself, there can be little doubt that the patches of emphysema, which are such a prominent feature of every case, are the result of these bronchiolar changes.

As early as two hours after exposure, there is histological evidence of necrosis of the epithelium of the finer bronchi. This is in contrast to the epithelium in the larger bronchi and trachea, which is well preserved, even the ciliated border remaining intact (Fig. 4). In the smaller bronchi, the mucous surface is covered by a thick layer of eosin-staining material, made up of mucus and desquamated epithelium (Figs. 10 and 11). Beneath this layer the cells are more or less flattened or rounded. The nuclei are either pyknotic or completely disintegrated. As a result, the exudate, mucosa, and wall of the bronchus all appear as a relatively homogeneous pink-staining mass in which very little structure is to be made out.

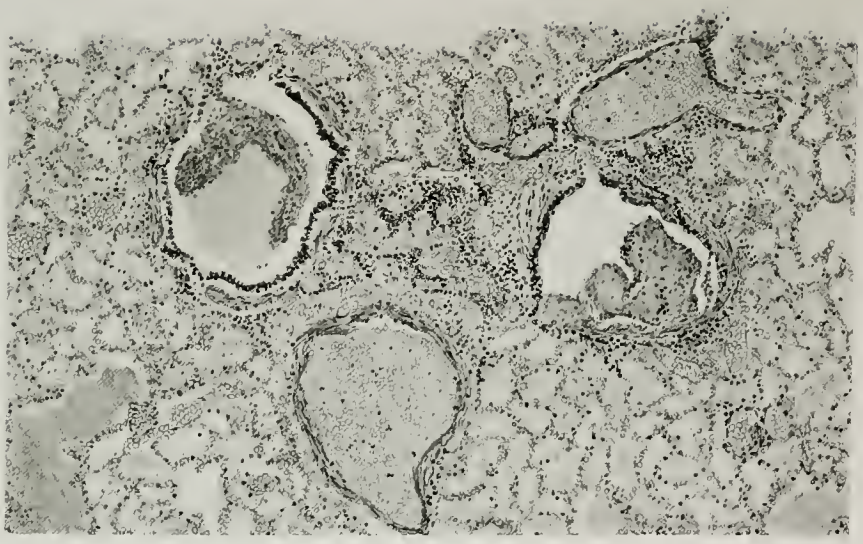

FIG. 10. LUNG OF DOG DYING 20 HOURS AFTER GASSING. THE TWO SMALL BRONCHI PRESENT SHOW PARTIAL DISINTEGRATION AND DESQUAMATION OF THEIR LIVING EPITHELIUM, AND AN EXUDATE OF MUCUS AND LEUCOCYTES IN THE SURROUNDING TISSUE.

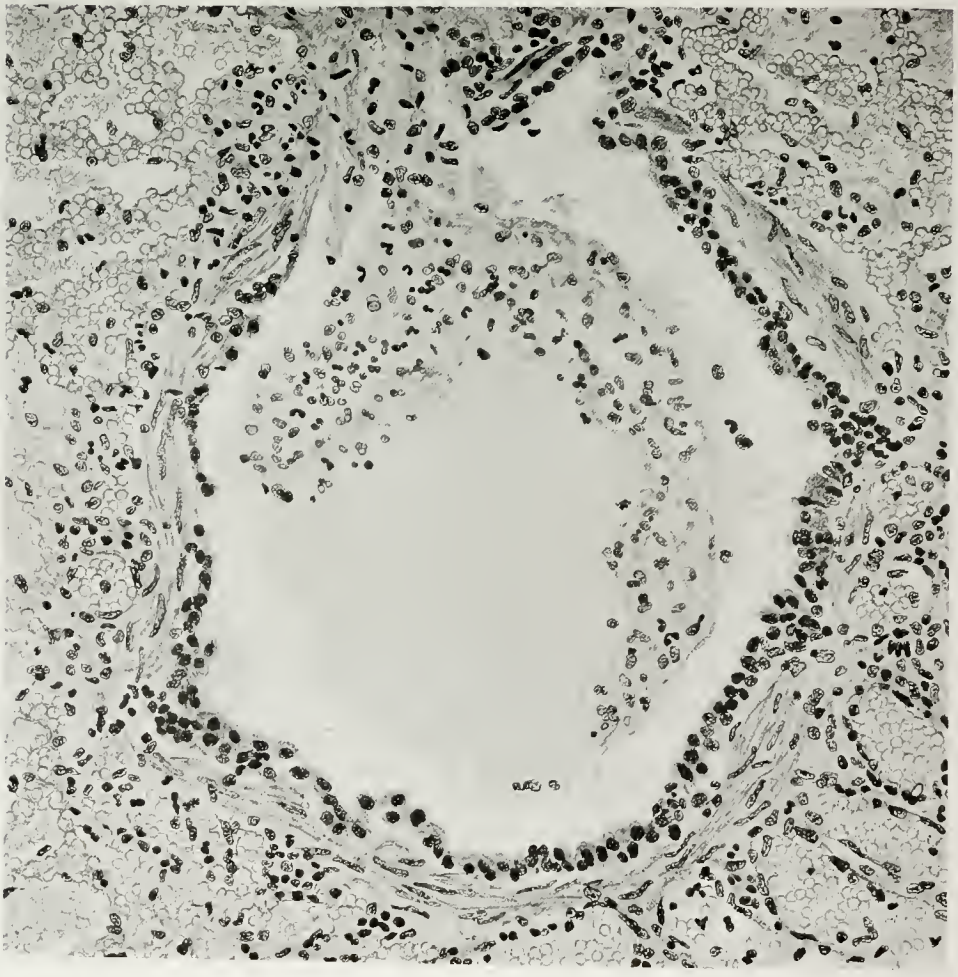

FIG. 11. HIGHER MAGNIFICATION OF ONE OF THE BRONCHI SEEN IN FIG. 10. NOTE THE EARLY INFLAMMATORY REACTION IN ONE PORTION OF THE WALL AND THE DEGENERATION OF THE LINING CELLS, WHICH HAVE LOST ALL THE CHARACTERISTICS OF BRONCHIAL EPITHELIUM.

Use of Vital Stains for Determining Cell Injury.

Conclusive evidence on the question of the difference in the degree of injury suffered by the proximal and distal portions of the respiratory tract in phosgene gassing, has been adduced by the use of vital stains.

It will be recalled that vital stains, when administered in sufficient quantity, stain the cytoplasmic granules of certain types of cells. The nucleus of the living cell is, however, never stained; whereas that of a dead cell is deeply colored. The reaction to the vital stain thus constitutes a delicate test of cell death.

In applying the test to the question of the time and place of the primary injury in phosgene poisoning, ten dogs were injected intravenously on two successive days with 100 cc. of a 1 per cent. solution of the dye, and then exposed for half an hour to phosgene gas at a concentration varying between 80 and 97 parts per million. These animals were sacrificed at intervals from 2 hours to 3 days after they had been gassed, and frozen sections, counter-stained with carmine, were made from different portions of the respiratory tract. The results may be stated briefly.

In no instance is the tracheal epithelium stained. On the other hand, the bronchial epithelium shows staining of its nuclei and protoplasm in places, and as the finer bronchioles are approached, the coloration becomes more marked and the change more uniform. Still, all bronchioles are not equally affected. Some show unstained epithelium; whereas others in the immediate vicinity stand out clearly by reason of the deep staining of their lining cells. The staining seems most marked where there is distortion of the bronchiole, either contraction or dilatation. The entire bronchiolar wall is involved, but the stain does not spread to neighboring alveolar walls, and the flat alveolar epithelium is unaffected. These results were obtained in animals that were sacrificed as early as two hours after exposure to the gas.

Inflammatory Reaction.

In many cases the bronchus forms the center of an inflammatory focus, which extends for a variable distance into the surrounding lung tissue (Fig. 12). Besides these focal lesions, there is evidence of a more general inflammatory reaction in the lungs. Nearly everywhere, there is an increase in the number of polynuclear leucocytes in the alveolar walls, and occasionally they are seen in process of migration into the alveoli. In addition, there is more or less fibrin in the alveolar exudate. The extent of this pneumonic process varies in different animals. Even animals that have been subjected to exactly the same concentration and that have survived approximately the same length of time, may show a great difference in the extent of the inflammatory reaction. In some cases it is entirely absent.

In Table III a few figures on this point are given. It is seen that approximately 50 per cent. of the animals dying in the first 48 hours showed a definite pneumonia. Whether or not the pneumonia or the associated edema is the chief cause of death in these cases, would be difficult to say; although in animals which survive this period and die 3 to 10 days after gassing, it is clear that the pneumonia is the more important factor.

The content of the blood vessels in the lung is in all cases simple post-mortem clot, which, however, is often rich in fibrin. We have not been able to demonstrate in the capillaries any definite hyalin thrombi such as Bunting has described. The presence of fibrin masses in the alveolar walls and crossing the capillaries, and its importance have been referred to already.

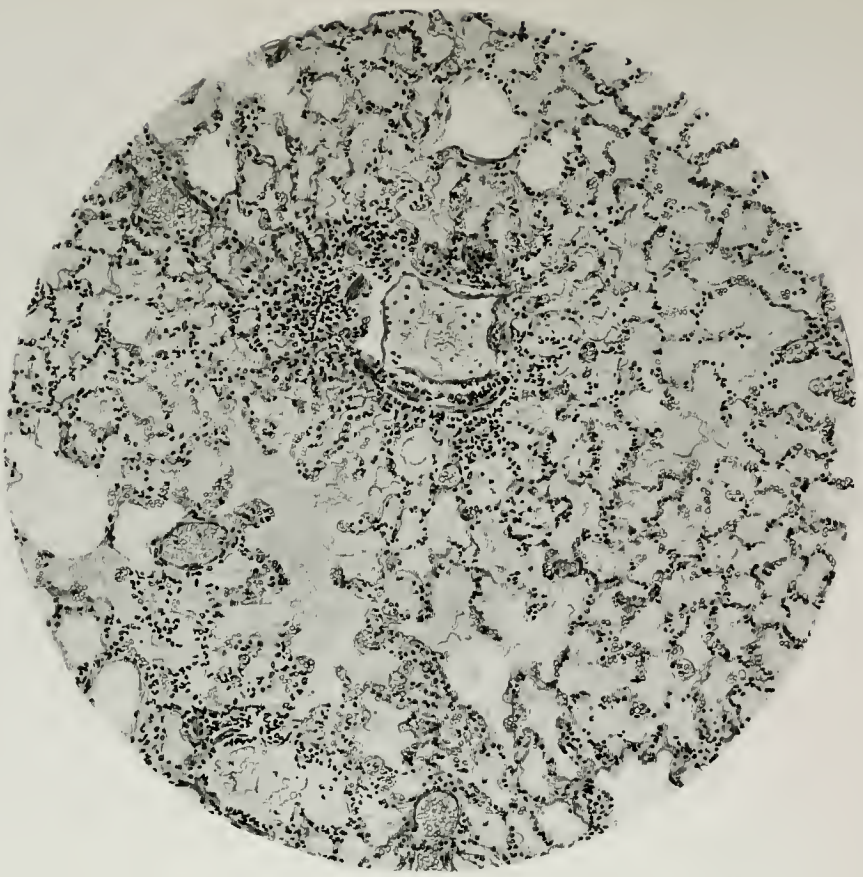

FIG. 12. EARLY INFLAMMATORY REACTION ABOUT BRONCHIOLE 18 HOURS AFTER GASSING. CELLS ARE CHIEFLY POLYNUCLEARS. SOME FIBRIN IS PRESENT, BUT IS NOT CLEARLY SEEN WITHOUT SPECIAL STAINS.

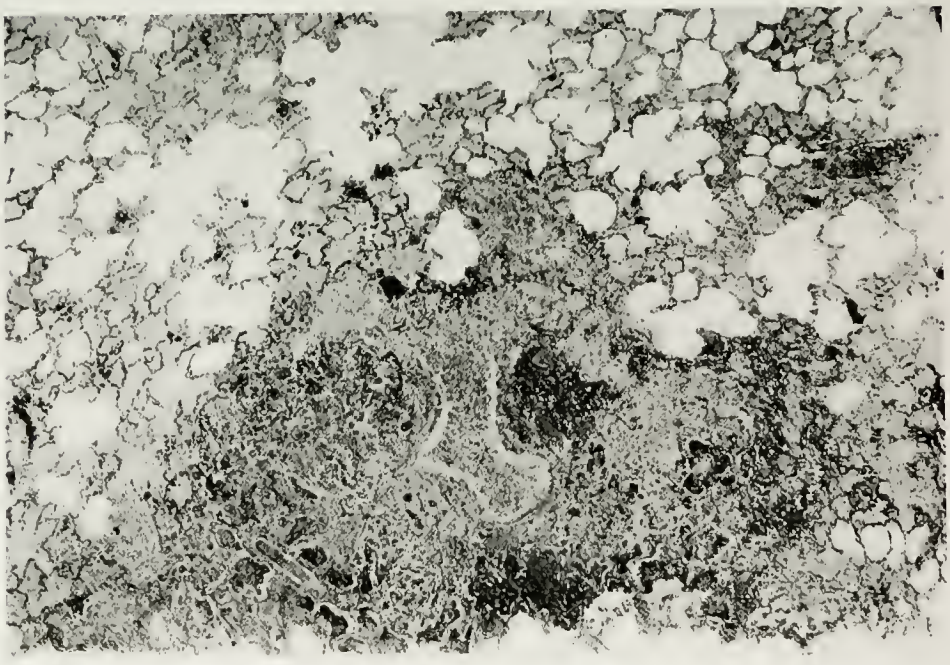

FIG. 14. BRONCHO-PNEUMONIA IN A DOG DYING 7 DAYS AFTER GASSING. THERE IS NECROSIS OF THE BRONCHIAL WALL AND HEMORRHAGE INTO THE PERIBRONCHIAL EXUDATE. THE LUNG TISSUE OUTSIDE THE PNEUMONIC ZONE IS EDEMATOUS.

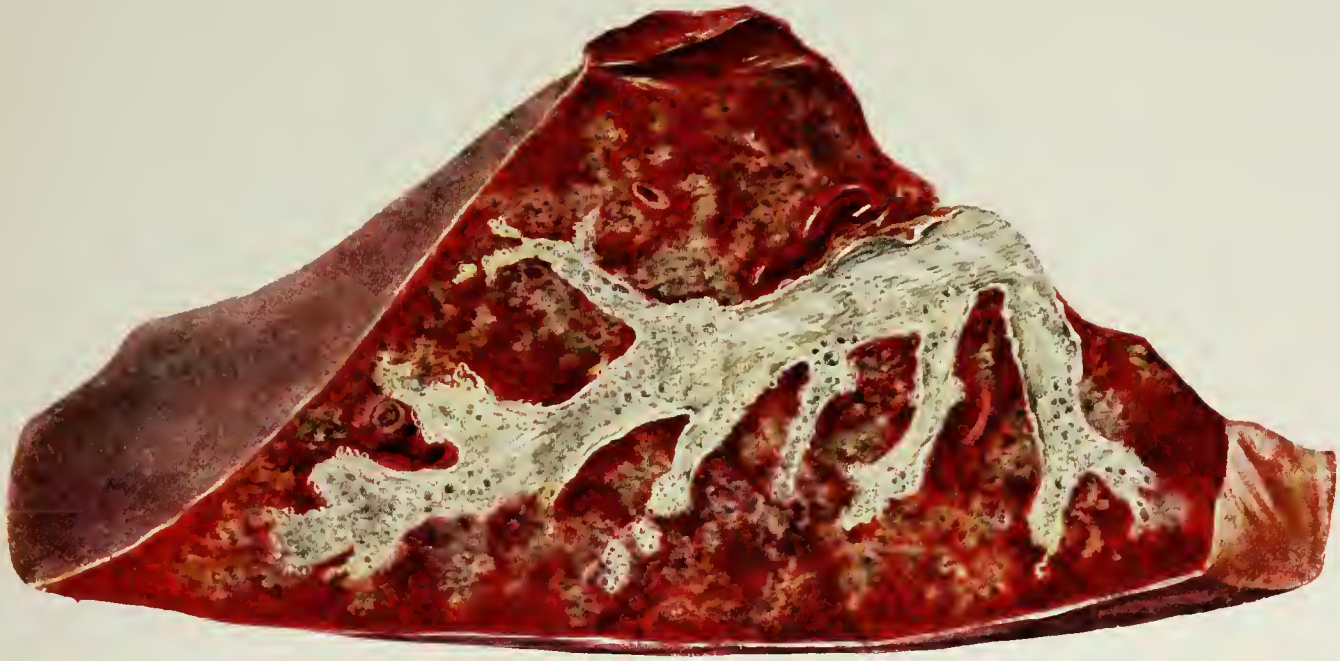

PLATE VIII

FIG. 13: BRONCHO-PNEUMONIA AND PURULENT BRONCHITIS IN DOG DYING 5 DAYS AFTER GASSING.

The adventitia of the larger vessels is spread apart by edematous fluid which is considerably richer in fibrin than that in the alveoli.

The *bronchial lymph glands* show a dilatation of their peripheral sinusoids, which contain mononuclear cells, red blood cells, and occasional polynuclear leucocytes. The channels through the glands are often spread apart much more widely than usual and show a similar cell content.

Liver: The hepatic vein in all instances is greatly distended, and this distension and engorgement may be present also in the portal vein. It is always more marked in the hepatic vein and in the capillaries which directly join this vessel. In this zone the liver cells are thinned out as though compressed, giving the typical picture of passive congestion as seen in man. There is, generally, no necrosis of the liver cells and no inflammatory reaction present. In a few cases, focal areas of necrosis were found, but on account of the rarity of this lesion, we have considered it accidental and not related to phosgene poisoning. In the same way, we have interpreted a single instance of hemorrhagic cystitis and of renal epithelial necrosis.

SUMMARY

The important *acute* changes brought about by exposure to lethal concentrations of phosgene gas are confined to the cardio-respiratory system. The upper respiratory tract is unaffected, and this is in marked contrast to the changes in the lungs and finer bronchi.

The lungs are the seat of an intense edema and congestion, which are associated in many cases with a focal inflammatory reaction originating apparently in the bronchioles. The inflammatory exudate is not confined to the bronchioles but spreads for a variable distance into the surrounding alveoli, so that a picture of an early broncho-pneumonia is found superimposed upon an extreme degree of edema of the lung. Dilatation, contraction, and plugging of the bronchioles with exudate, lead to a patchy atelectasis and emphysema. The presence of an abundance of fibrin on and in the alveolar walls, crossing and obstructing the capillaries everywhere, offers an explanation for the increased resistance to the pulmonary circulation and the consequent dilatation of the right side of the heart.

GROUP II. *Animals Dying or Killed 3 to 10 Days After Gassing. Subacute or Intermediary Period.*

This group comprises 66 dogs, of which 15 were killed, and 51 died. There is a much greater variation in the pathological picture, gross and microscopic, among the animals dying in this period than in the earlier and more acute stage, where, as we pointed out, there is certain monotony, especially in the gross features. On account of this variation, it will be necessary in describing the findings to subdivide the cases further into (*1*) those which died and (*2*) those that were killed.

In the animals that died the anatomical changes are characterized by the presence of a severe and widespread inflammatory process in the respiratory tract. Thus Table III shows that in 90 per cent. pneumonia was found at autopsy, and bronchitis in 96 per cent. A brief note on the gross anatomical findings will suffice.

Gross Anatomical Findings in Animals Dying in Subacute Stage.

Externally, the body presents nothing abnormal. The eyes are not injected, and fluid rarely escapes from the mouth.

In the abdominal cavity there is little worthy of note. The splanchnic engorgement

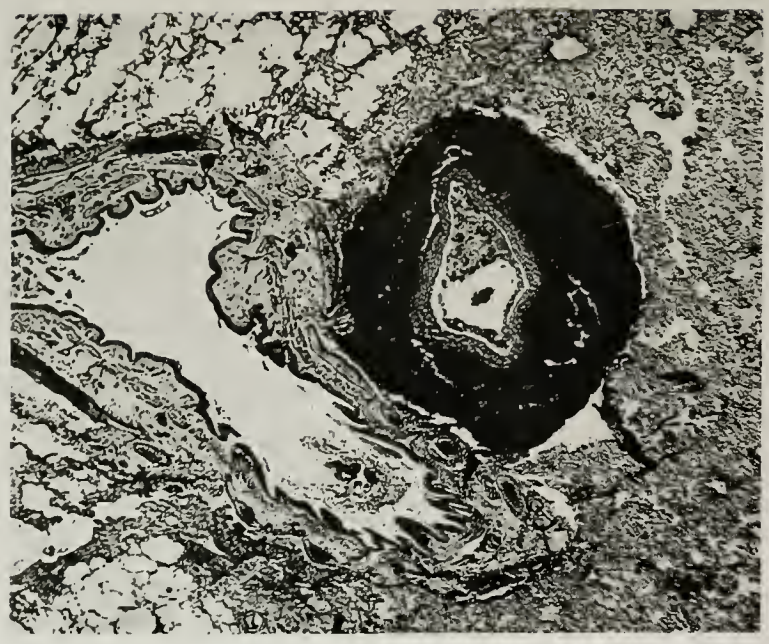

FIG. 15. HEMORRHAGE INTO PERIVASCULAR SHEATH IN DOG DYING 10 DAYS AFTER GASSING.

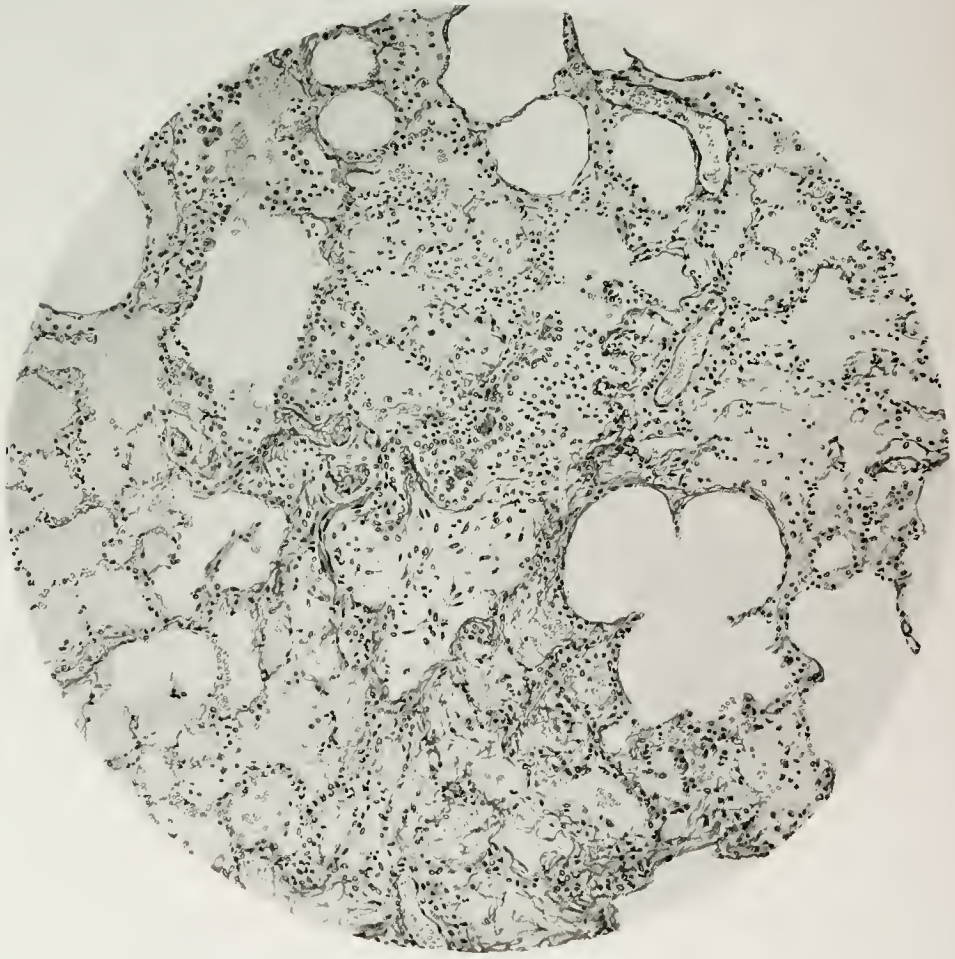

FIG. 17. BEGINNING ORGANIZATION OF INFLAMMATORY EXUDATE IN BRONCHIOLE 4 DAYS AFTER GASSING. THERE IS AN ABUNDANCE OF FIBRIN IN ALVEOLAR WALLS EVERYWHERE. POLYNUCLEAR LEUCOCYTES ARE NUMEROUS IN THE EXUDATE.

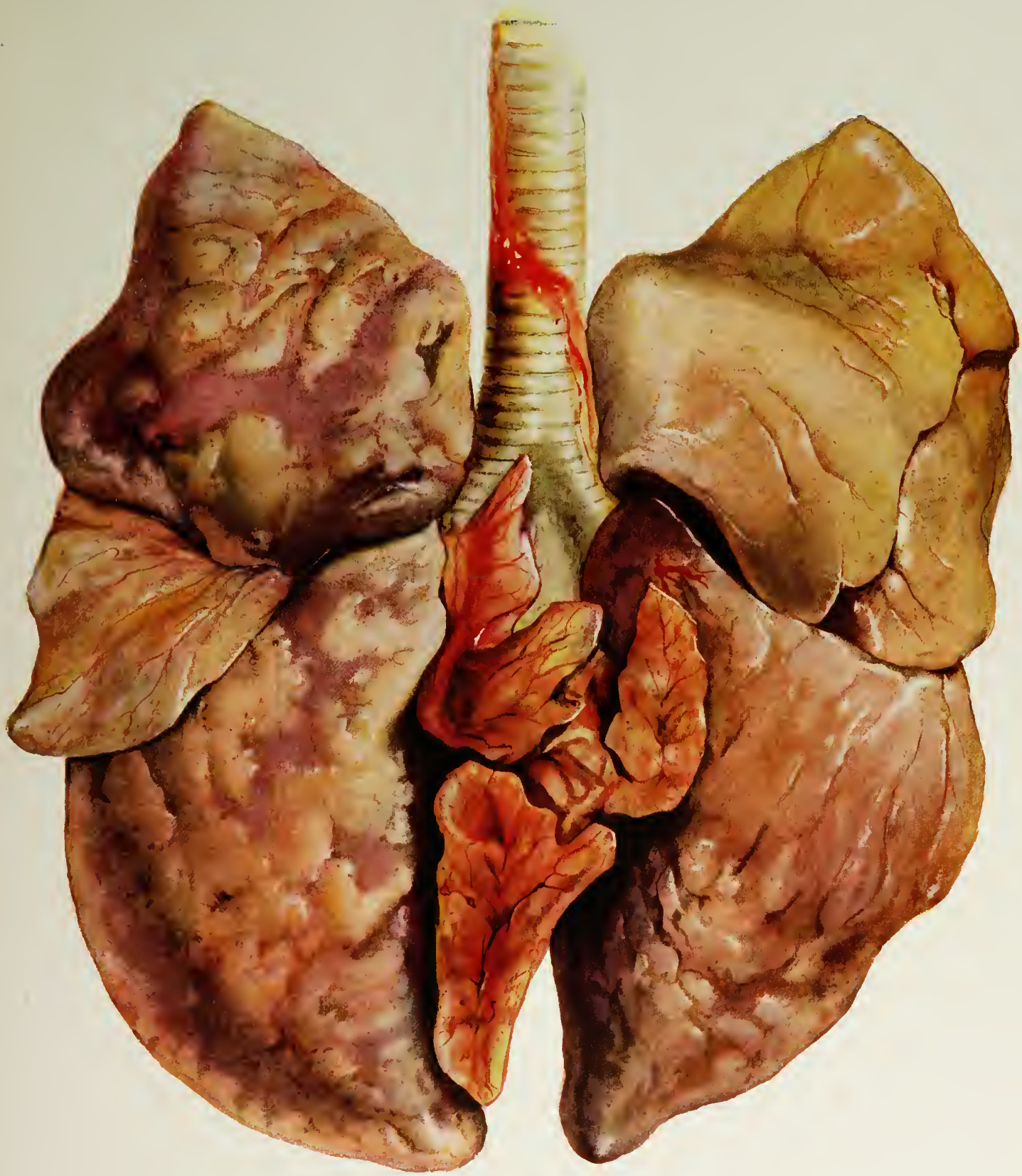

PLATE IX

FIG. 16: LUNG OF DOG KILLED 14 DAYS AFTER GASSING. THERE IS MARKED EMPHYSEMA WITH IRREGULAR PATCHES OF ATELECTASIS. MICROSCOPICALLY, A WIDE-SPREAD OBLITERATIVE BRONCHIOLITIS IS FOUND.
(SEE FIG. 19.)

is still to be seen, and the large, purple liver extends somewhat lower in the abdomen than usual. The pleural cavities are not as well filled as in the acute period, but the lungs are still voluminous. The pericardial and pleural surfaces are generally smooth and glistening. In a few cases there is a slight excess of straw-colored fluid in the sacs. In one instance this was excessive, and in another the fluid was purulent.

The *heart* is dilated, as in the earlier period, and the dilatation involves principally the right side. An abundant chicken-fat clot, of the usual translucent quality, is generally present, in contrast to the red clot, so regularly seen in the acute deaths. No thrombi have been encountered.

The endocardium is normal, except for the occasional presence of subendocardial hemorrhages such as were described in Group I. They are rarer here, however, than in the animals dying more acutely.

The upper respiratory tract, including the larynx and trachea, is practically normal in appearance. The *trachea* and larger *bronchi* present a pale, grayish-white surface on which there is only an occasional dilated vessel, but the smaller bronchi, examined from above downward, become progressively more inflamed and dilated. Many are plugged with an exudate, which is sometimes opaque and yellowish, in other instances, translucent and mucopurulent in character. The dilated bronchi can be traced sometimes to the pleura where they end in rather wide sacs just beneath the surface. This is true, however, of only those portions of the lung which are not extensively involved in the pneumonic process.

The *lungs* are very voluminous. The surface is smooth; but, very frequently, firm, pale pinkish areas, often irregularly wedge-shaped, stand out in sharp contrast to the remaining portion of the lung, which is cushiony and crepitant. In animals that survive only three days, these solid areas are not as prominent a feature as in animals that live longer. In practically all cases, the consolidation is more pronounced in the thinner lappets and near the edges of the lung than in the body of the organ. The posterior and lower portions of the lung may be involved in the pneumonic process, but, as a rule, these parts, which in the early deaths show the greatest edema, are not so regularly consolidated. It may be recalled in this connection that it is the upper lobes which are the more dependent in dogs and other four-footed animals.

The lobes vary considerably in weight. They are all heavy, but pneumonic lobes naturally outweigh those which are the seat of edema and congestion only.

Perivascular edema is still to be made out around the larger vessels of the hilus. In the *vessels*, only post-mortem clots are found; no thrombi are present. The *bronchial lymph glands* at the hilus are large and succulent. The *bronchi*, as stated before, contain viscid exudate.

On section, the lungs vary in their appearance according to the length of survival of the animal. In the more acute deaths, the lungs are still very wet, and it may be difficult to make out the areas of consolidation which later stand out as dry, granular areas that vary in size from a few millimeters to many centimeters. The dry, granular areas are dark and reddish brown in color, not nearly as translucent as the areas of edema and congestion, and very much firmer. In the smaller patches of consolidation, there is almost always a central bronchiole, which is prominent on account of its thickened wall and a purulent exudate in its lumen (Fig. 13). In animals surviving longest, the areas of consolidation stand out much more clearly, and may involve the greater portion of a lobe, although as a rule only one-third to one-half of the lobe is affected. This consolidation is not confined to one lobe, and, not infrequently, three or more lobes may contain extensively hepatized areas. The con-

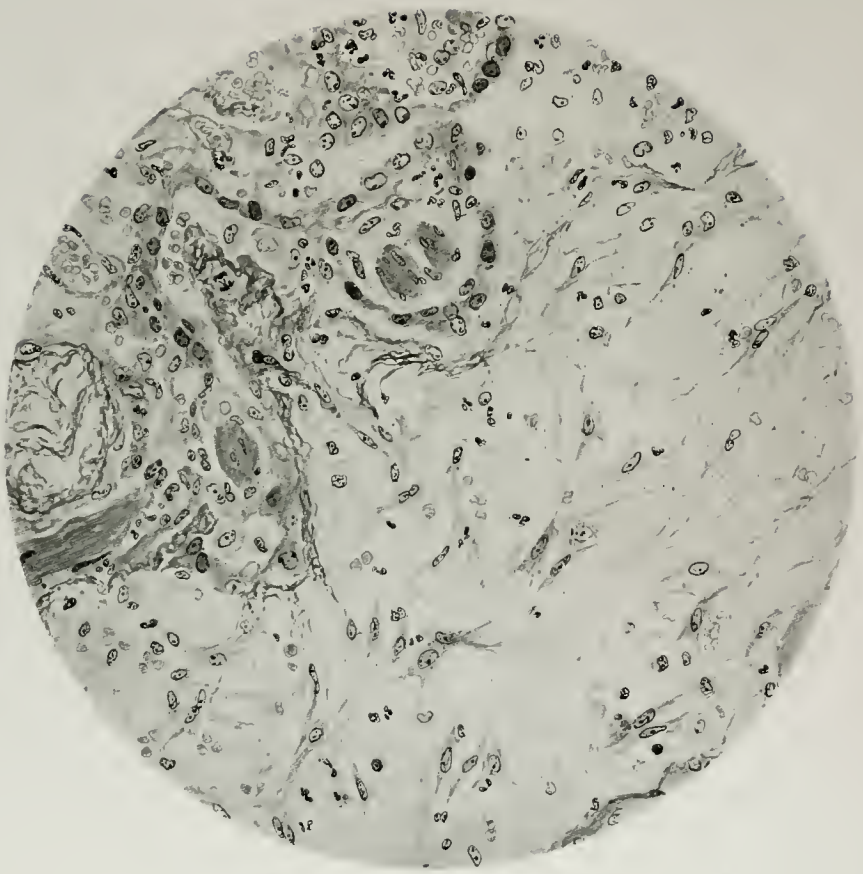

FIG. 18. HIGHER MAGNIFICATION OF SAME SHOWING ACTIVE GROWTH OF FIBROBLASTS. ONE IS SEEN ON LEFT IN PROCESS OF DIVISION.

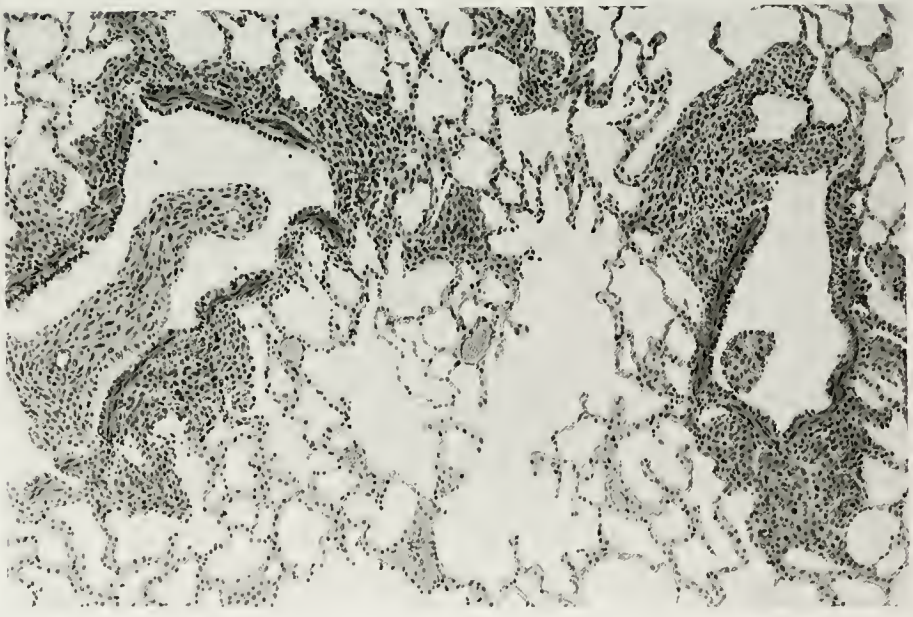

FIG. 20. HIGHER MAGNIFICATION OF FIG. 19.

solidation is pseudo-lobar in type. Small areas of broncho-pneumonia may be seen scattered in the less diffusely consolidated portions of the lung.

Microscopic Findings. .Histological studies corroborate the gross findings. With the exception of a few subsidiary lesions in the abdominal organs and heart, the chief interest lies in the respiratory tract. As might have been expected from the gross appearance, the trachea shows practically no change. In a few instances slight congestion of the vessels of the submucosa without cellular exudate is noticed. Further down, where the bronchi are surrounded by lung tissue, the picture becomes much changed. The epithelium is in part desquamated and is mixed with an exudate of red and white blood cells and mucus in varying proportion.

In all instances, the bronchioles exhibit very striking changes. They show no foldings. In other words, they are dilated and appear as large, round holes, filled with exudate. The word "holes" is used advisedly, since it is not easy to determine whether structures which look like bronchioles are in all instances such. In many places, they have lost their identifying epithelium, and on account of the lack of structure in their walls, they do not present any characteristic, histological features. The epithelium is sometimes still distinguishable but is usually desquamated and mixed with an exudate of red cells and polynuclear leucocytes. This inflammatory exudate generally extends for some distance into the surrounding alveoli. In many instances the alveoli, two or three rows deep about the bronchiole, have lost their architecture, the walls being obscured by the leucocytic infiltration. At the periphery of such a broken down area, which is essentially a miliary abscess, there is a zone of hemorrhagic pneumonia (Fig. 14). The lining epithelium stains poorly, and in many alveoli, the cells have become desquamated and lie free in the alveolar spaces.

The pneumonic zone fades rather abruptly into areas where the lung tissue is well preserved. The alveoli here may be partially collapsed or emphysematous. Their walls are always prominent on account of the dilatation of the vessels and the partial desquamation of the alveolar epithelium. The alveoli in this zone contain some fibrin and serum with occasional desquamated cells and leucocytes. That this is a very early inflammatory process is evident from the large number of polynuclear leucocytes caught in process of migration from the vessels.

The pneumonia is often widespread, approaching a lobar distribution; but the character of the reaction is still that of a lobular pneumonia, and it is clear that the infection in these cases, as in the less extensive pneumonias, is bronchial in origin. Organization of the exudate is seen now and then, but is a much more common finding in dogs that were killed and are to be described later.

Microscopic findings outside the respiratory system are of little interest. In the *liver*, the changes are very similar to those described in Group I. The congestion in the hepatic vein persists, and frequently the liver cells in the immediate vicinity are reduced to fine strands, with the intervening sinusoids greatly congested. These liver cells contain brown pigment, but very rarely is there any nuclear disintegration or leucocytic infiltration. The *kidneys* show cloudy swelling of the tubular epithelium, and, occasionally, the glomeruli may be markedly congested, but there is no evidence of any permanent damage to the renal parenchyma.

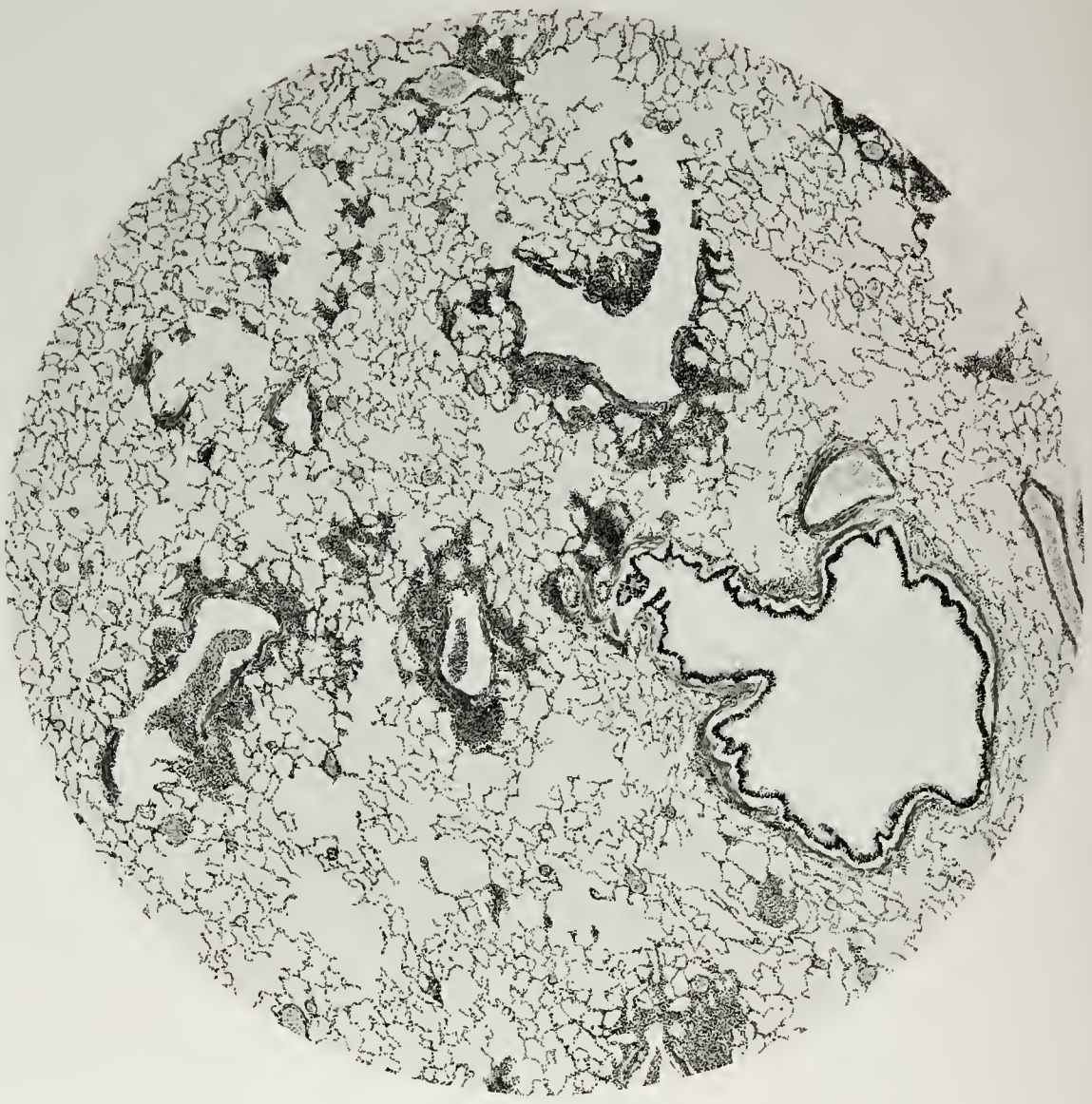

FIG. 19. LATER STAGE OF ORGANIZATION IN AND ABOUT BRONCHIOLES. DOG KILLED 14 DAYS AFTER GASSING. LUNG SHOWED GROSSLY PATCHES OF EMPHYSEMA AND ATELECTASIS.

Bacteriological Findings. The bacteriology of the pneumonias following gassing with phosgene was investigated in 23 cases with the following results:

Streptococcus hemolyticus was found alone in 10 cases.

Staphylococcus aureus alone in 6 cases.

Streptococcus and staphylococcus together in 3 cases.

Streptococcus and other organisms in 2 cases.

Miscellaneous or undetermined organisms in 2 cases.

It is seen that a hemolytic streptococcus was the most common organism met with, being demonstrated in 13 out of 23 cases. It has not been possible to show a relationship between the type of organism present and the character of the pneumonia, although we have gained the impression that abscess formation and organization are more often associated with the staphylococcus than with other organisms. It may be of interest to note that in a few cases of pneumonia among non-gassed dogs autopsied about the same time, the bacteriological findings were roughly the same as in the gassed animals.

Gross Anatomical Findings in Animals Killed in Subacute Stage.

Fifteen dogs were killed from the 3rd to the 10th day after gassing in order to see what change the lung is undergoing in animals which pass successfully the stage of congestion and edema, and which have apparently escaped or recovered from the pneumonic infection, fatal to so many of the other animals in the same experiment. Only animals in good condition were selected for this study, with the object of getting those that were really on the road to recovery.

The *gross changes* in the lungs in these dogs are most interesting and distinctly different from those seen in the acute period. However, some of the earlier lesions, congestion, edema, and emphysema, are still present in moderate degree. Of these the edema is the most marked, though much less so than in the Group I dogs.

The most striking gross feature of the lungs is the presence of small nodules, which are scattered throughout all lobes. They can be felt only vaguely on account of the associated edema and emphysema. On the cut surface, they are more readily palpated and can be seen easily as small gray semi-translucent foci, which, in their distribution, correspond to the small bronchi. Indeed, a small bronchial opening can be made out sometimes in the center of the nodule. From the 3rd to the 5th or 6th days, the nodules are not as sharply outlined nor as translucent and firm as they become later. Not infrequently, they are made prominent by the presence of hemorrhages in their substance, which naturally changes the usual gray color to a bright red.

Microscopically, we found in one or two of the cases a definite early pneumonia, not different from that seen in the dogs that died. In two others there was a wide zone of organization about the smaller bronchi, which was interpreted as a healed or healing pneumonia. In all the rest the picture was the same, namely, a widespread, organizing bronchitis and bronchiolitis (Figs. 17 and 18). Under very low magnification, one sees a patch of cellular tissue about almost every bronchus, especially the smaller. The tissue is composed of young fibroblasts, few capillaries, and many mononuclear wandering cells. In quite a number of the bronchi there is an exudate undergoing organization, with permanent obliteration of the lumen.

Fibrin stains show that there is often considerable old fibrin in the midst of the organizing areas. This, according to Mallory's ideas, might be regarded as the stimulus for organization.

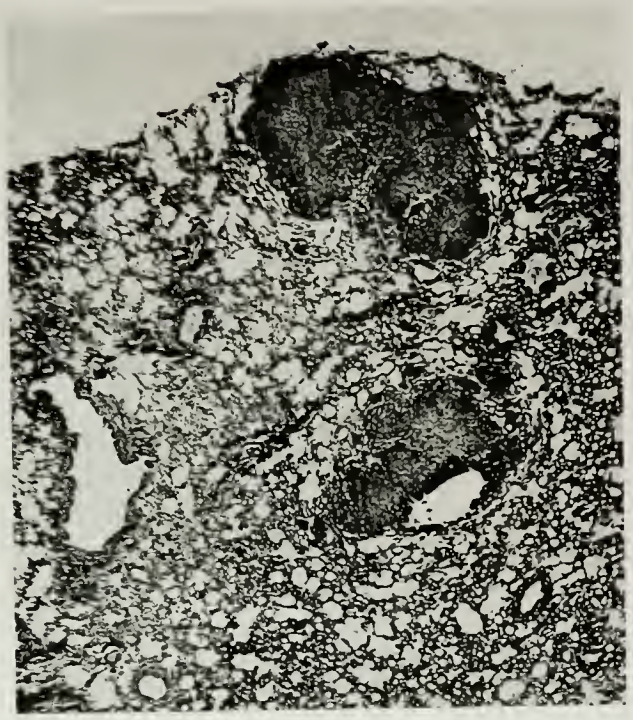

FIG. 21. MILIARY PERIBRONCHIAL NODULES IN DOG DYING 33 DAYS AFTER GASSING. THE NODULE IS MADE UP OF FIBROBLASTS, LARGE MONONUCLEAR WANDERING CELLS AND FEW BLOOD VESSELS.

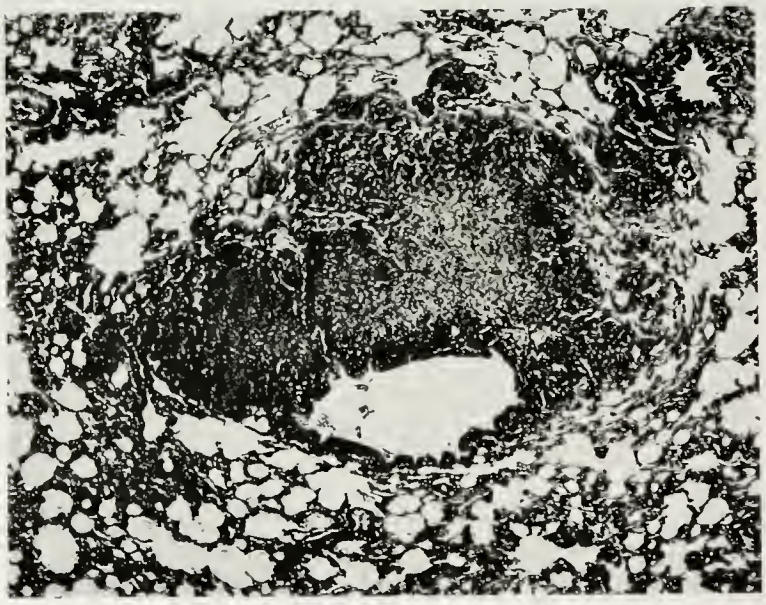

FIG. 22. HIGHER MAGNIFICATION OF ONE OF NODULES SHOWN IN FIG. 21.

Polynuclear leucocytes and fresh fibrin are not present in any quantity in the typical cases, which suggests that the infection (bronchitis or broncho-pneumonia of the early period) to which these lesions undoubtedly are a sequel, has been successfully combated.

SUMMARY

When death is delayed 3 to 10 days after exposure to phosgene gas, infection of the respiratory tract is the cardinal change found. The upper air passages remain practically unaffected except for a mild congestion, but there is intense necrotizing infection of the bronchioles, which not infrequently involves the surrounding alveoli and results in the formation of miliary abscesses. These are surrounded by a narrow zone of hemorrhagic pneumonia. The intervening lung tissue shows alveoli filled with varying amounts of serum, fibrin, and cells. If death is delayed more than four days, beginning organization of the exudate in the alveoli and bronchi is generally seen.

If animals which have apparently recovered from the acute symptoms following gassing and which give no signs of pneumonia are killed 3 to 10 days later, they show a widespread, organizing bronchiolitis, which clearly represents the sequel of the acute bronchial and peribronchial inflammatory reaction, so prominent in the acute period.

GROUP III. *Animals Dying or Killed 11 to 129 Days After Gassing. Chronic Period.*

There is a total of 177 dogs in this group, of which 69 died and 108 were killed. Description will be made easier and clearer if the "died" and "killed" dogs are considered separately. It may be pointed out, however, that some of the animals that were killed looked sick and in poor condition and would have died in a few days had they been left alone. As might be expected, the lesions found in such animals are practically the same as in those that died.

The pathology of the dogs that died differs little from that observed in the 5- to 10-day animals, already described.

The essential and dominating feature in a majority of the cases is an infection of the respiratory tract. A glimpse at Table III shows that in 50 per cent. of the cases pneumonia of one type or another was present, and bronchitis in 75 per cent. It can be safely stated that death was referable to respiratory infection, acute or chronic, in at least 65 per cent.

What, may be asked, is the cause of death in the remaining 35 per cent? In a few cases, there was a chronic nephritis of the type not infrequently met with in dogs, which may have been responsible. In the other 20 to 25 per cent. no cause of death was found. These animals were all poorly nourished and anemic; parasites of various kinds were present in the intestines; but this was true also of practically all of the "killed" animals as well. In other words, we failed to demonstrate lesions sufficient to account for death in at least 15 to 20 per cent. of these chronic dogs. It is possible, of course, that a careful study of the blood-forming organs or endocrine glands, not as yet investigated in any of our cases, may throw some light on the question.

A majority of the dogs which were killed were well nourished and appeared healthy. Some were thin and sluggish; a few were in bad condition and obviously about to die. The findings in these sick dogs were referred to in the previous paragraph, and need not be taken up again.

The gross changes in the healthy looking animals are not very striking. Aside

from the lungs, there is little worthy of note. The trachea and larger bronchi are quite normal.

The *lungs* are moderately collapsed, but the collapse is not uniform. Figure 16 illustrates very well the picture often seen. There are dark pink atelectatic patches here and there; the rest of the lung tissue is more or less emphysematous. Tiny firm nodules may be felt or seen on section, but these are not at all conspicuous. Hemorrhages in the nodules and elsewhere in the lung are common, and "ring hemorrhages" about the vessels are frequently seen (Fig. 15). The bronchi are more prominent than normally. Their walls look thickened, and in the lumina, there is an excess of mucus.

Microscopically, the picture is somewhat more varied and interesting. The emphysema and atelectasis are more pronounced than in the gross. The alveoli show no other change. The bronchi show a more marked alteration. There is a distinct fibrous thickening of the walls of some of the medium-sized bronchi, and an infiltration by mononuclear wandering cells most marked in the outer coat. This lesion we have termed a peribronchitis. The tubercle-like nodules noted in the gross specimens sometimes look very much like tubercles, microscopically (Figs. 21 and 22). In a large number of cases, the only change found is in the small-sized bronchi. Here the lumen in places is completely occluded by a mass of granulation tissue, and there is a zone of similar cellular connective tissue immediately about the bronchus (Figs. 19 and 20). This lesion, which is a perfect example of obliterative bronchiolitis, clearly represents a more advanced stage of the organizing bronchiolitis and pneumonia found in dogs killed 3 to 10 days after gassing. These changes in the bronchi are quite sufficient to account for the persistence of the atelectasis and emphysema, which is seen to be directly proportional to the extent of the bronchial lesions. The susceptibility of these chronic gassed dogs to pneumonia is also probably referable to the presence of such foci of infection in the bronchial wall.

Our interest in this latter question, led us to make cultures from the lungs in 31 cases in which no gross or microscopic evidence of pneumonia was found, that is, in dogs showing only the chronic lesions just described.

The bacteriological findings may be summarized as follows:

Staphylococcus aureus	5 cases
Streptococcus hemolyticus	5 cases
Streptococcus non-hemolyticus	2 cases
B. subtilis	4 cases
Miscellaneous organisms	5 cases
No growth	10 cases
	31

It is seen that the lungs were sterile in less than a third of the cases, while pathogenic organisms were present in probably 40 to 50 per cent. These findings afford an explanation for the tendency of these recovered dogs to develop a fatal pneumonia even months after gassing.

CONCLUSIONS.

The result of phosgene poisoning in dogs finds its chief anatomical expression in the respiratory tract. The lesions seen at autopsy vary according to the length of time the animal survives after gassing.

At first there is a severe pulmonary edema associated with extreme congestion, which reaches a maximum toward the end of the first 24 hours and disappears gradually in animals surviving 10 days or longer.

The edema is associated with an inflammatory exudation of fibrin and leucocytes, which is most marked in and around the finer bronchioles, and which spreads to a variable extent throughout the lung tissue. A typical lobular or pseudo-lobar pneumonia is the result.

The pneumonia is frequently complicated by a necrotization of the wall of the bronchus, which may involve the adjacent alveoli to form an abscess. On the other hand, the inflammatory process may be combated successfully, but in the healing, foci of organizing pneumonia and obliterative bronchiolitis result. Bacteriological studies show that these lesions constitute chronic foci of infection.

The character of the phosgene lesion is explained by the localization of the action of the gas upon the air tubes. The epithelium of the trachea and larger bronchi is not damaged, while that of the smaller bronchi and bronchioles is seriously injured, the more distal portion suffering most. In addition to the changes in the mucosa, the bronchi also show pathological contractions and distortions, which result in more or less complete obliteration of their lumina. These, in turn, lead to mechanical disturbances in the air sacs, resulting in atelectasis or emphysema.

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TABLE I

	Time of death after gassing	*Total cases*	*Died*	*Killed*
Group I.	1 to 12 hours	29	29	0
	12 to 24 "	197	195	2
	2nd day	34	32	2
Group II.	3rd "	23	20	3
	4th "	16	11	5
	5th "	8	8	0
	6th "	7	4	3
	7th "	3	2	1
	8th "	3	3	0
	9th "	1	1	0
	10th "	5	2	3
Group III.	11th "	0	0	0
	12th "	5	3	2
	13th "	4	3	1
	14th "	3	3	0
	15th "	2	0	2
	16th to 129th day	163	60	103
		503	376	127

TABLE IA

	Animals dying	*Died*	*Killed*	*Total cases*
Group I.	First 48 hours	256	4	260
Group II.	3rd to 10th day	51	15	66
Group III.	11th to 129th day	69	108	177
		376	127	503

TABLE II

Decree of Increase in Lung Weight after Gassing

Animals died	*No. cases averaged*	*Increase based on Lung-heart ratio*	*Lung-body ratio*
First 12 hours	10	2.32	2.53
12 to 24 hours	65	2.50	2.84
2nd day	13	2.40	2.74
3rd day	10	2.64 *	3.31
4th day	6	2.36 *	3.32
5th to 10th day	7	2.20 *	2.92
11th to 104th day	21	2.23 *	2.51
Animals killed			
5th to 10th day	4	1.47	
11th to 104th day	25	1.13	1.20

* These figures do not indicate the degree of edema present, since practically all of the animals

TABLE III

		Pneumonia Per Cent				Bronchitis Per Cent			
	Animals dying	*All types*	*Early*	*Advanced*	*Organizing*	*All types*	*Early*	*Advanced*	*Organizing*
Group I.	First 48 hours	48	48	0	0	59	57	2	0
Group II.	3rd to 10th day	90	12	53	25	96	20	48	28
Group III.	11th to 129th day	50	12	26	12	75	6	53	16
	Animals killed								
Group I.	First 48 hours	50	40	10	0	50	40	10	0
Group II.	3rd to 10th day	23	8	0	15	100	0	100	0
Group III.	11th to 129th day	9	6	0	3	68	2	32	34

dying at this period had pneumonia. The cellular exudate in the lungs would account for the larger share of the increased weight of the organ.

NOTE ON THE COMPARATIVE PATHOLOGY OF ACUTE PHOSGENE POISONING

BY

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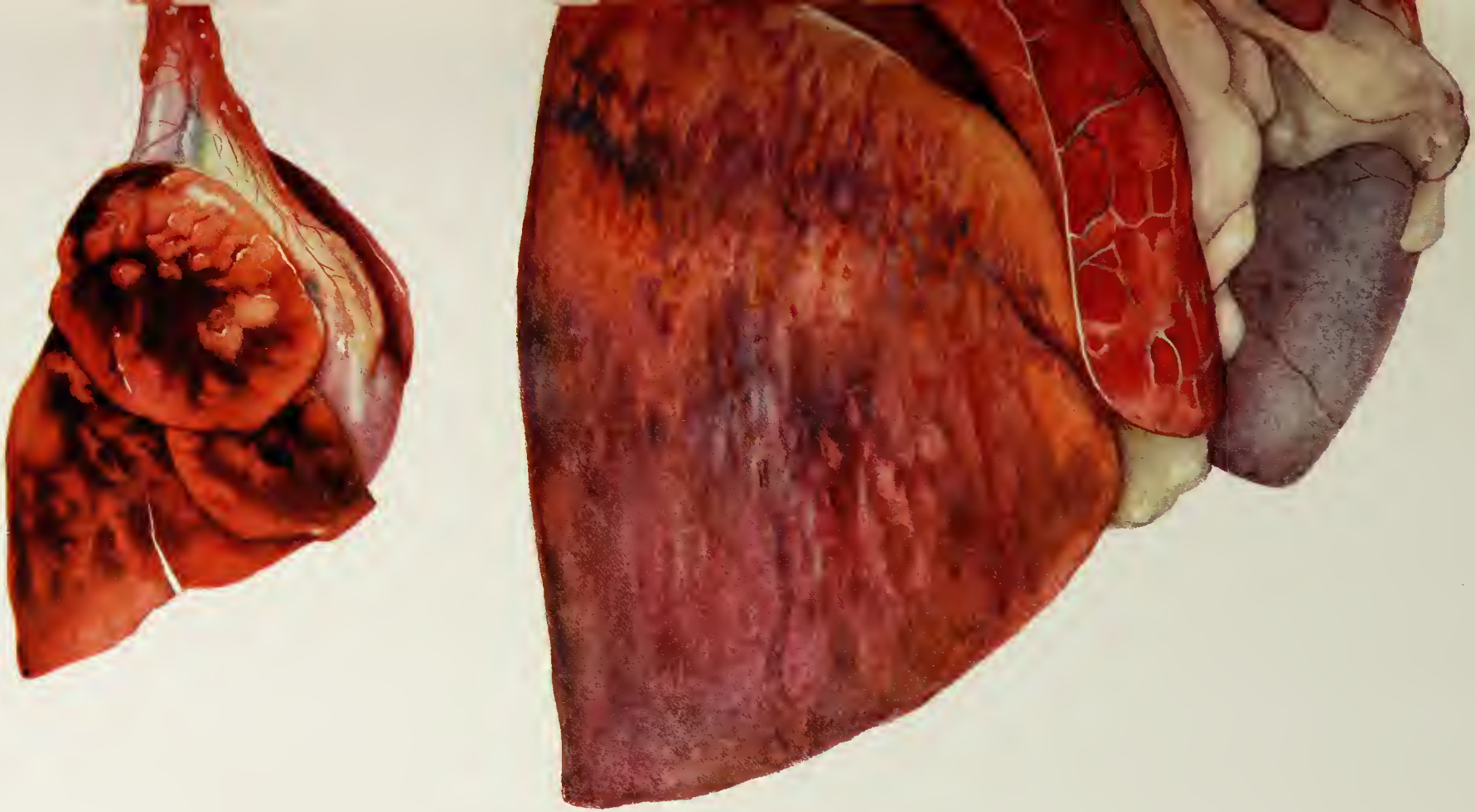

PLATE X

FIG. 1: LUNGS OF GOAT, MONKEY AND GUINEA PIG AFTER EXPOSURE TO PHOSGENE. (CONC. 0.27, DURATION 30 MIN.) THE MONKEY DIED 3 HOURS, 15 MIN., THE GUINEA PIG 3 HOURS, 20 MINUTES AFTER GASSING. THE GOAT WAS KILLED 12 HOURS AFTER EXPOSURE.

NOTE ON THE COMPARATIVE PATHOLOGY OF ACUTE PHOSGENE POISONING

THERE is a well-known degree of latitude among animal species as regards susceptibility and tolerance towards toxic substances. Neglect of such considerations has frequently led to false deductions from one species to another and especially from animals to man. In studying the toxicology and pathology of poisonous gases, it is, therefore, important to determine the degree of species variation for each gas.

At the present time, very few data exist on the comparative toxicology and nothing upon the comparative pathology of phosgene.

The following tables from English reports * indicate the susceptibility of various species of animals to phosgene.

Concentration of phosgene (mgm. per liter) required to kill at the stated time intervals.

	3 minutes	*15 minutes*	*30 minutes*
Rabbit		0.88	0.44
Goat	2.2		0.44
Dog	2.2	0.88	0.44
Cat	1.6		0.22
Rat	0.88		0.08
Guinea pig	0.88		0.08
Monkey	0.44		0.08

In a second report, the lethal concentration of phosgene for different species of animals at a three-minute exposure is given as follows:

Species	Dog	Cat	Rat	Goat	Rabbit	Monkey	Guinea pig
Conc.	1.5	1.5	0.9	2.2	5.0	0.4	0.9

A series of experiments was performed where a number of different kinds of animals were exposed in the same chamber for 30 minutes to a concentration of 0.27 mgm. per liter of phosgene. The time of survival varied as indicated in the table below.

Species	*Survived*
Monkey	3 hrs. 30 min.
Guinea pig	4 hrs. 30 min.
Rat	5 hrs.
Rabbit	11 hrs. 30 min.
Mouse	Killed after 12 hours
Dog	" " " "
Goat	" " " "

* Abstract by Capt. E. K. Marshall, C. W. S., March, 1918.

The lesions produced in these animals by inhalation of phosgene are essentially alike.

In the monkey and goat, for example, which represent the two extremes of susceptibility after exposure to the same concentration, lesions of the lung vary in degree but not in character. The species variation, evidenced by the length of survival after gassing, depends in part upon the rate at which edema develops. On the other hand, some animals (monkey, guinea pig), the first to succumb to a given concentration, show less pulmonary edema than those that survive longer (dog, goat). This is evidence, as is brought out elsewhere just as clearly,* that the edema is itself not the cause of death but simply one manifestation of a more important underlying change.

While pulmonary edema develops more rapidly the more susceptible the species—monkey to goat—these animals, that is the most susceptible, show less edema than the more resistant ones.

This is an indication of the importance of the time interval in the production of the edema.

There are no essential differences in the pathology of phosgene poisoning in different species, and the picture has been fully described in the preceding report on the effects of the gas on the dog.

SUMMARY

The pathology of phosgene poisoning in the goat, dog, monkey, rabbit, guinea pig, rat, and mouse is similar. The important lesions are confined to the lower respiratory tract. These consist essentially of an edema filling many of the alveoli, associated with inflammatory changes, which begin in the bronchioles and extend into the alveoli.

Toxicological experiments demonstrate a well-marked species variation towards phosgene, which finds its chief expression in the pathological picture as a difference in the amount of edema. Although edema develops more rapidly in the more susceptible species, it does not attain the degree commonly found in those animals which survive the same concentration for a longer interval. This not only emphasizes the time factor in its production but also clearly indicates that edema in itself is not the cause of death.

* See Chlorpicrin.

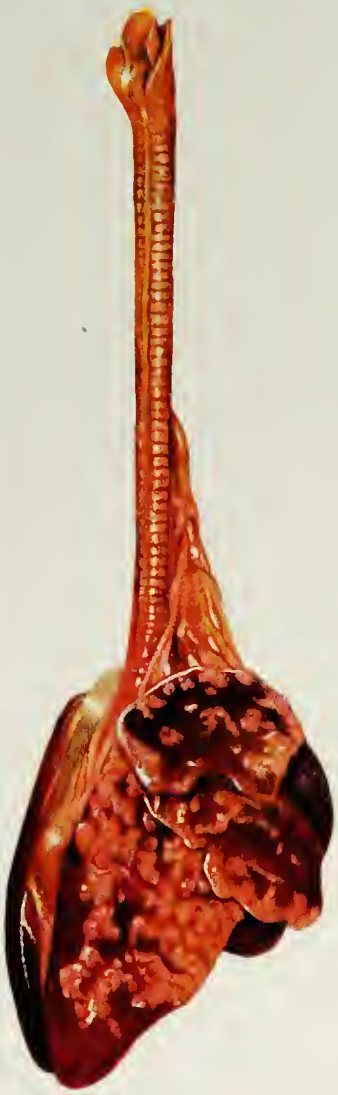

PLATE XI

FIG. 2: LUNGS OF RABBIT EXPOSED TO PHOSGENE. (CONC. 0.22, DURATION 30 MIN.) DIED AFTER 12 HOURS.

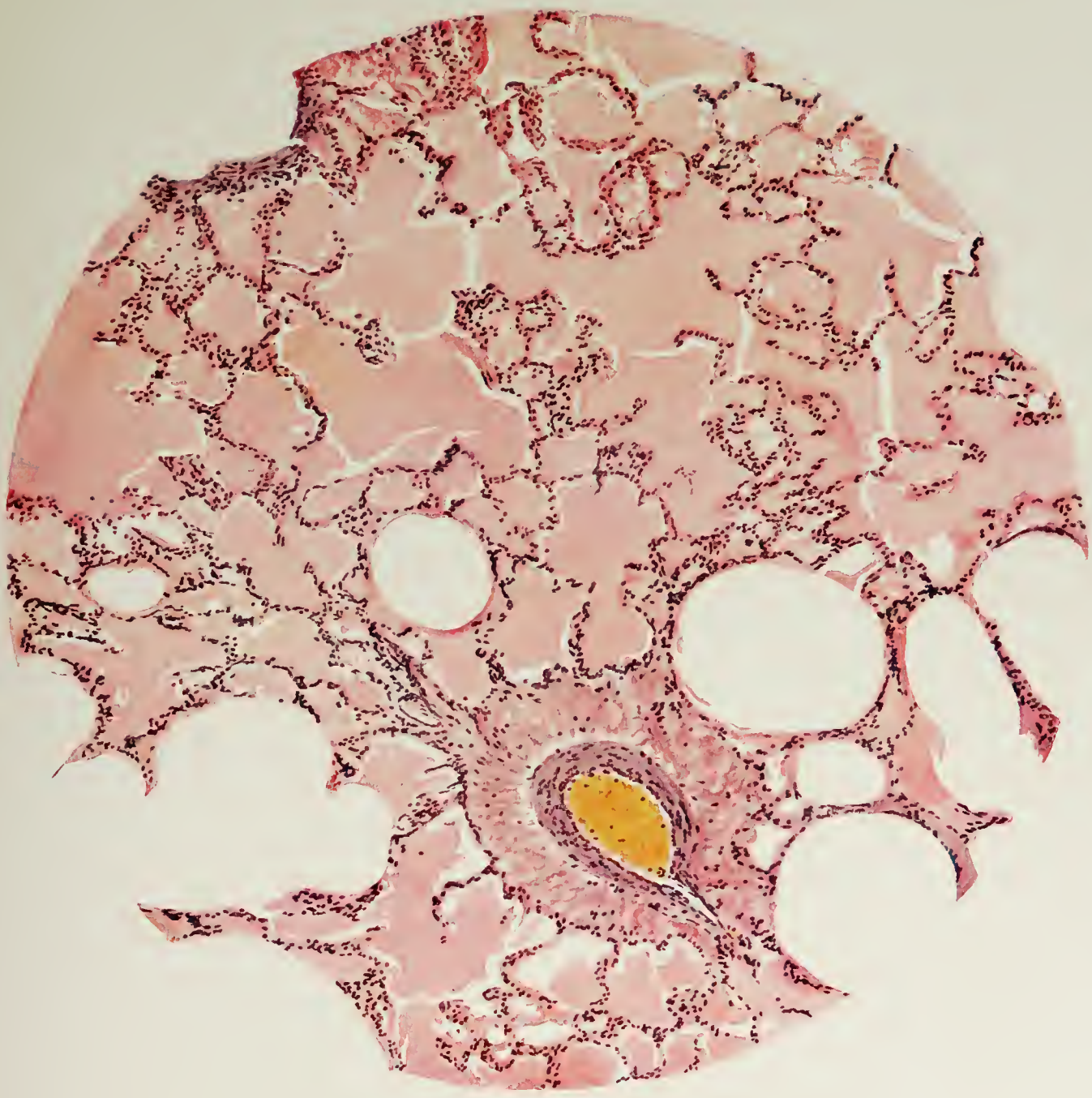

PLATE XII

FIG. 3: CROSS SECTION OF LUNG OF MONKEY SHOWING EDEMA. GROSS APPEARANCE OF SAME LUNG IS SHOWN IN FIG. 1.

THE PATHOLOGY OF CHLORPICRIN POISONING

BY

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THE PATHOLOGY OF CHLORPICRIN POISONING

Chlorpicrin, $CCl_3 NO_2$, belongs to both the lachrymatory and respiratory irritant groups of war gases. Even in relatively low concentrations, it induces an active flow of tears. Exposure to high concentrations causes severe damage to the respiratory tract followed by extreme edema of the lungs, similar to that produced by chlorine and phosgene.

Chlorpicrin also causes nausea and vomiting, and it is chiefly this action of the gas that has led to its wide use in modern warfare and given it the popular name of "vomiting gas." Being a very stable and non-absorbable substance, it penetrates masks more readily than many other of the noxious gases. Having passed through the protecting canister, it forces the soldier, by its nauseating effects, to tear off his mask and thus expose himself to other more toxic gases, such as phosgene, against which he was adequately protected while wearing the mask.

This tactical use of chlorpicrin is one reason why it is so often combined with other more deadly gases. A second reason lies in the fact that chlorpicrin is not strictly speaking a gas, but a liquid with a fairly high boiling point (112° C.), and is, consequently, not readily diffusible at ordinary temperatures. Satisfactory diffusion is obtained only by mixing it with more volatile substances or explosives.

EFFECTS OF CHLORPICRIN ON MAN AND ANIMALS

SYMPTOMATOLOGY

In gas warfare, as just stated, chlorpicrin is practically always used in combination with other gases. It has, therefore, proved difficult for medical officers to distinguish the effects of the several members in these combinations. However, accidents in gas manufacturing plants, with exposure of workmen to liquid chlorpicrin or the fumes, have served to demonstrate some of its effects.

More exact information has been gained from the experimental gassing of animals.

It has been shown that application of liquid chlorpicrin to the human skin produces severe, deep burns, and that a drop of it in the eye may cause ulceration of the cornea.

The fumes are likewise quite irritating to the skin and mucous membranes, and the exposed surface shows sooner or later a marked inflammatory reaction, often suppurative in character, owing to the superimposed bacterial infection.

In man, inhalation of the gas causes, almost immediately cough, nausea, and vomiting, and if the concentration is sufficiently high, or the exposure prolonged, dyspnea, cyanosis and weakness develop, with unconsciousness and death in a few hours. Though the initial symptoms may not be very severe, death may come after three or four days, as the result of respiratory infection. Among other complications, nephritis has been reported, though in animals experimentally gassed, evidence of injury to the kidney has not been found.

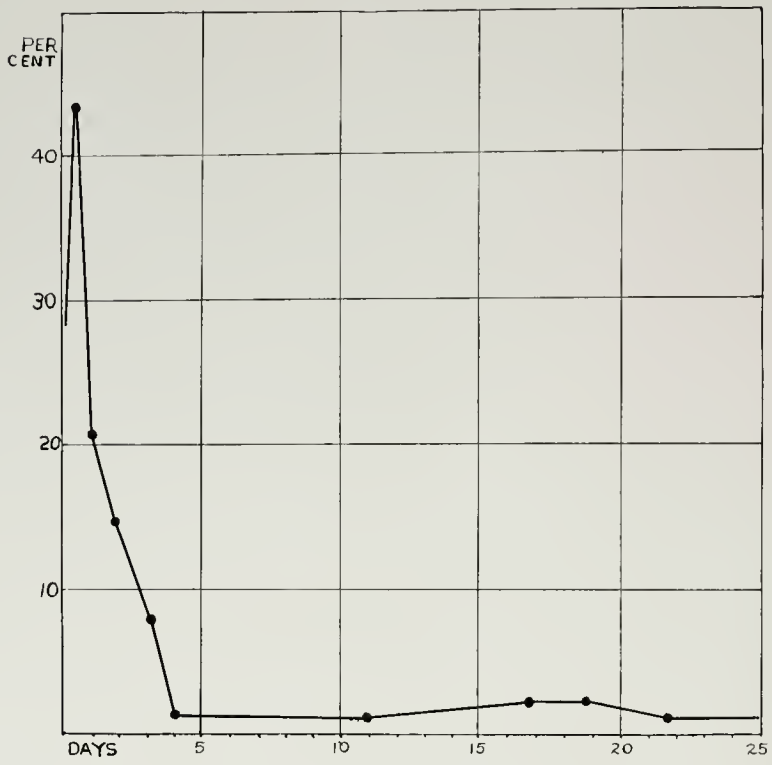

CHART I. CURVE BASED ON NUMBER OF DEATHS OCCURRING DAILY AFTER GASSING. IT IS SEEN THAT THE PEAK OF THE CURVE IS REACHED IN LESS THAN 12 HOURS, AND THAT IT FALLS ABRUPTLY AFTER 24 HOURS, ALTHOUGH DEATHS CONTINUE FOR MORE THAN 20 DAYS AS THE INDIRECT RESULT OF THE GASSING. THE CURVE, OF COURSE, WOULD NOT BE APPLICABLE TO A SERIES OF ANIMALS SUBJECTED TO HIGHER OR LOWER CONCENTRATIONS THAN THOSE USED IN THESE EXPERIMENTS.

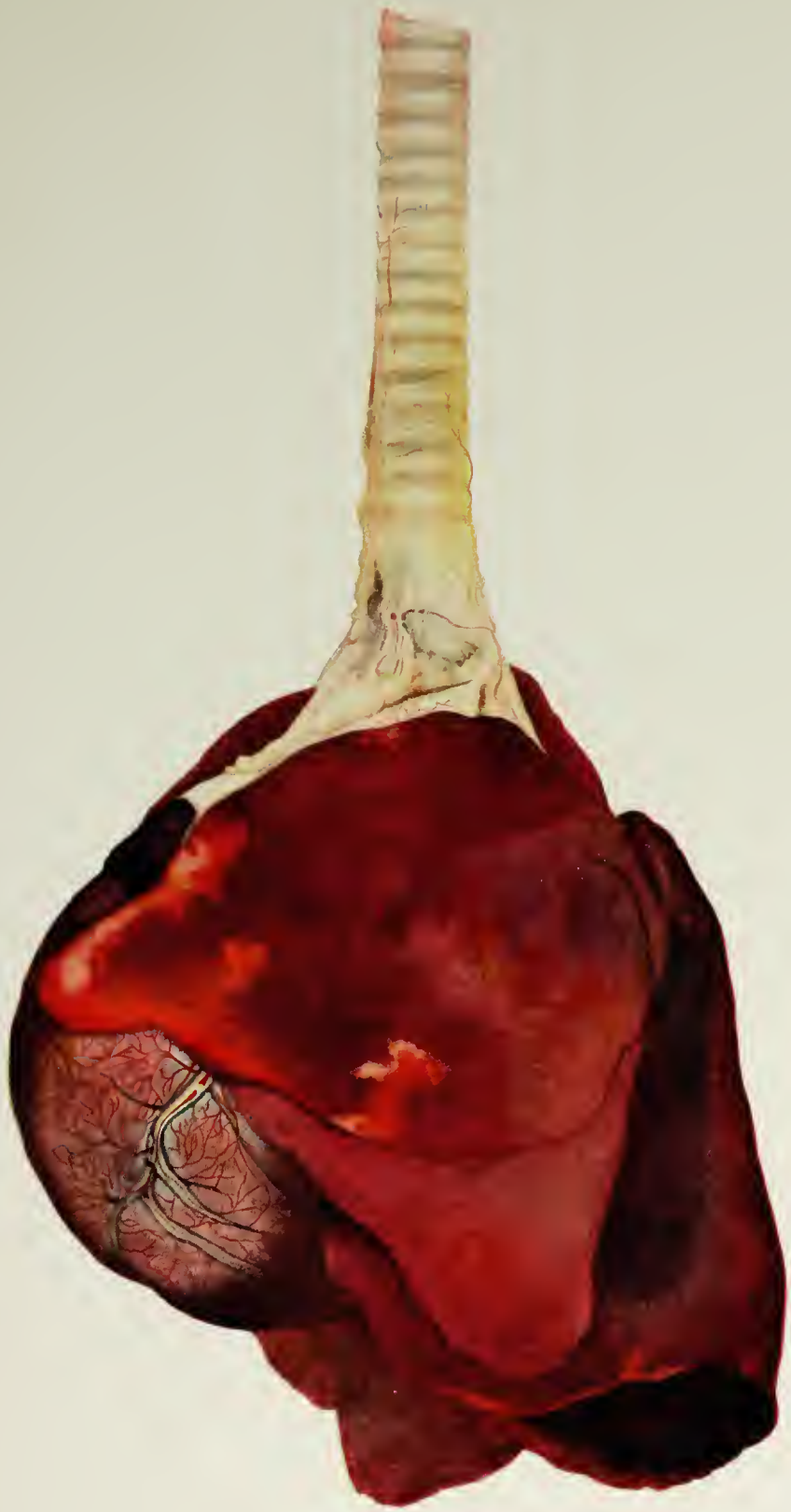

PLATE XIII

FIG. 1: HEART AND LUNGS OF DOG DYING 12 HOURS AFTER CHLORPICRIN GASSING. THERE IS EXTREME EDEMA OF LUNGS AND DILATATION OF HEART. NOTE ABSENCE OF ACUTE EMPHYSEMA.

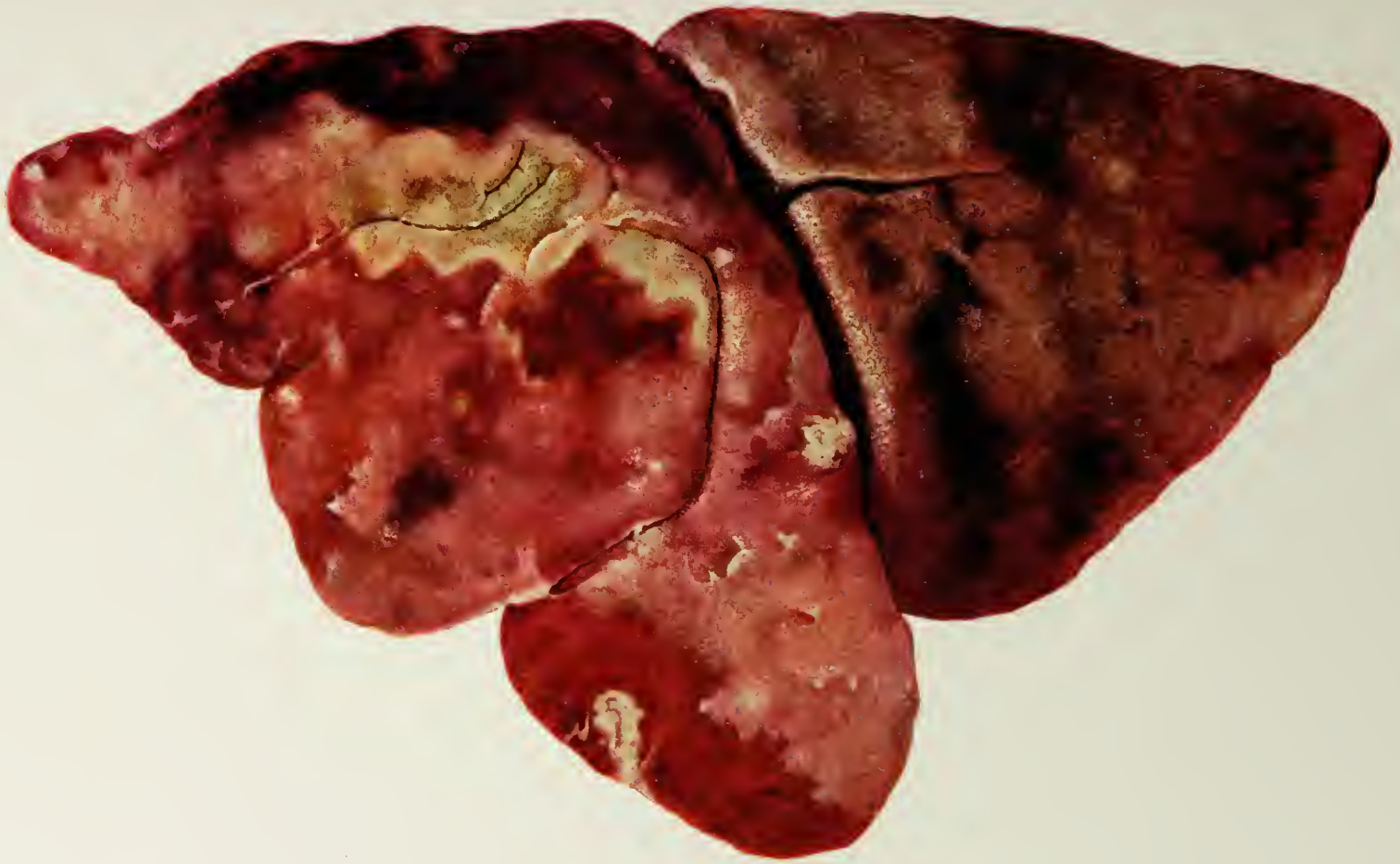

PLATE XIV

FIG. 2: BRONCHO-PNEUMONIA AND PURULENT PLEURISY IN DOG DYING 7 DAYS AFTER GASSING.

Marshall and Miller give the following description of the symptoms noted in dogs during and after exposure to lethal concentrations.

Symptoms During Exposure: The eyes are immediately irritated and lachrymation occurs during the early part of the exposure. After a short time, the animal usually keeps the eyes tightly closed. The mucous membranes of the nose and mouth are irritated almost instantly, the animal licking its nose and swallowing frequently. There is always increased nasal secretion and usually salivation, and in cases where salivation cannot be observed, the animal may be swallowing the saliva. Usually, retching and vomiting take place about ten or fifteen minutes after the beginning of the exposure with the higher concentrations. With lower concentrations, the animal does not always retch. Toward the end of the exposure, the animal is usually depressed, and in some cases marked pallor of the mucous membrane of the mouth is observed. The respiration is usually early affected, being somewhat rapid in the early part and becoming slow at the end.

Subsequent Symptoms: A tracheal rattle develops soon after exposure; respiration is labored and painful. There is usually a discharge from the nose and eyes. The animal often has a bad cough, and is generally depressed. Convulsions have been observed just before death. In case of survival, with the concentrations used, the dog has symptoms of bronchitis and rhinitis for a few days and then is apparently normal.

PATHOLOGY

We have been unable to find in the literature any reports of the lesions produced in man by chlorpicrin, except brief references to burns of the skin and mucous membranes, as noted above; and although considerable experimental use has been made of the gas, there are only fragmentary records of the findings in animals. In view of this and the more pertinent fact that chlorpicrin is being extensively used in the fighting at the present time and is likely to be more widely employed, it has seemed to us important that an adequate description of the anatomical and histological changes caused by it should be made available.

To do this is the purpose of the present paper.

As stated in the introduction by Major Winternitz, the co-operation of Lieut. Col. Underhill has made it possible for us to autopsy a large number of animals gassed in the Laboratory of Physiological Chemistry of Yale University in the course of certain therapeutic studies carried on by him and his assistants. Among the animals turned over to us, there have been up to the present time approximately 120 chlorpicrin dogs. A majority of these were animals that died shortly after gassing, but there were a number that succumbed 2 to 20 days later, and others that were killed at various intervals up to 26 days after gassing.

Table I shows the number of animals dying at varying periods after gassing, and in Chart I there is a curve based on these figures. It is seen that, as after exposure to corresponding lethal concentrations of chlorine and phosgene, the greatest number of deaths occur in the first 24 hours. The first part of the curve is like that of chlorine in that the peak is reached in the first twelve hours and not in the second twelve hours as with phosgene. However, there is not the secondary rise on the 3rd and 4th days noted in the chlorine series.

No figures as to the number of animals which survived gassing are given. But it may be stated in a general way that with low concentrations the per cent. of survivors is fairly

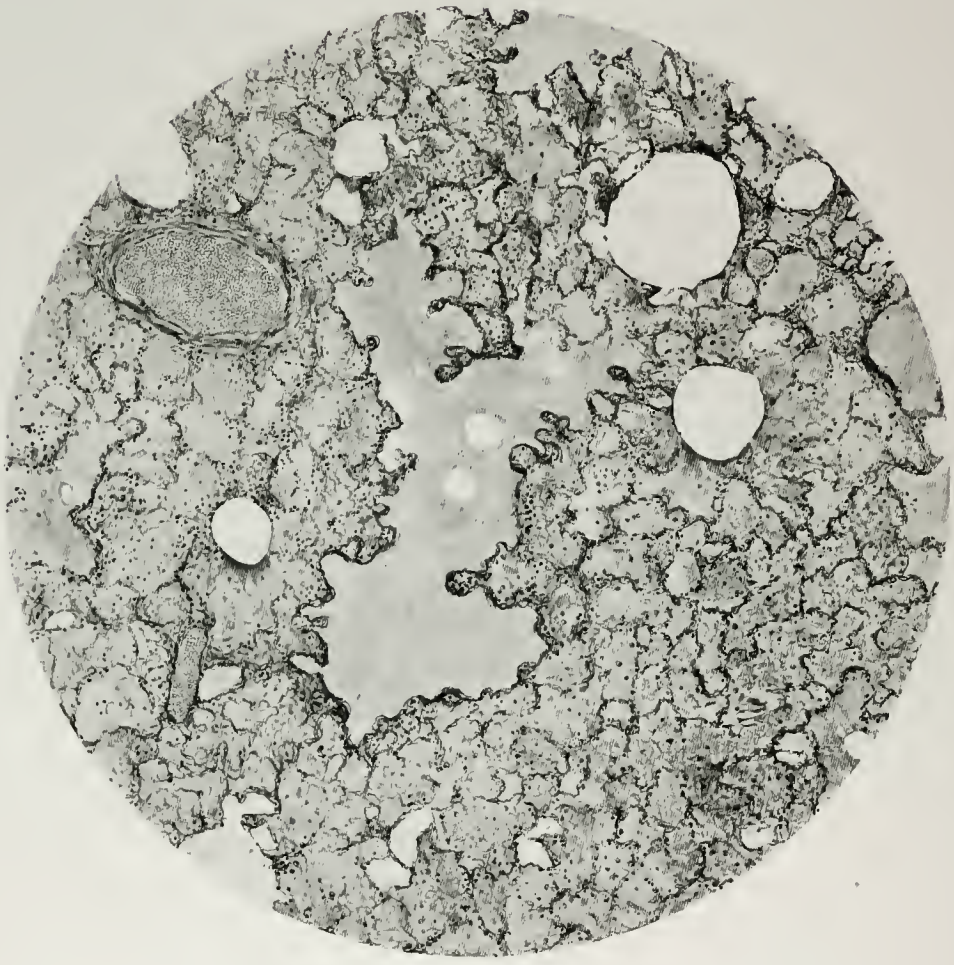

FIG. 3. WIDESPREAD EDEMA OF LUNGS IN ACUTE STAGE. THERE IS AN ABUNDANCE OF FIBRIN IN ALVEOLAR WALLS.

high. However, in most of the experiments, the concentration varies between 0.900 and 1.050 mgm. per liter, which in a half hour's exposure (the time allowed in every case) kills more than 50 per cent. of the dogs gassed.

For details regarding the toxicity of chlorpicrin in different concentrations, the reader is referred to papers by Underhill and his assistants, published elsewhere.

AUTOPSY FINDINGS

The changes found at autopsy are, as might be expected, quite similar in many respects to those associated with gassing by chlorine and phosgene and other members of the respiratory irritant group.

Since in preceding papers the pathology of chlorine and phosgene has been taken up rather fully, we shall make frequent reference in the following description to differences and similarities in the lesions produced by those gases and chlorpicrin.

We may conveniently divide the discussion into the findings in animals dying (*1*) in the acute stage and (*2*) in the subacute and chronic periods.

DEATH IN ACUTE STAGE

We have applied the expression "acute stage" somewhat arbitrarily to the first 24 to 48 hours after gassing, during which time the signs and symptoms are chiefly those of edema of the lungs, without clinical evidence of infection.

The following protocol will illustrate very well the usual findings at this period:

Young Airedale, female, Wt. 11.1 Kilos. Gassed 9/26–1918.

Concentration, 1,035 mgm. per liter; 30 min. in chamber.

Typical symptoms during and after gassing: lachrymation, retching and vomiting, depression. Later, viscid frothy discharge from mouth and nose, rapid and labored breathing, restlessness. Death, 15 hours after gassing.

Autopsy, three hours after death.

Body: Well nourished, but flanks and abdomen are shrunken. Weight is 700 gm. less than at time of gassing. Body is lax; there are beginning post-mortem changes.

Abdomen: Negative, except for engorgement of veins and congestion of liver. The congestion disappears as vessels are cut, the organ assuming normal color, with usual distinct lobulation.

Thorax: The cardiac area is large; the pericardial sac is tense, being stretched by the distended heart. Lungs are bulky, but do not tend to overlap the heart. There is a slight excess of fluid in pleural cavities and pericardium. Tissues about the great vessels are slightly blood-stained.

Heart: Weighs, full of blood, 130 gm.; empty, 83 gm.; heart-body ratio is approximately .008, that is, about normal. The right side is more distended than the left. Chambers are filled with red clot.

The heart valves are normal. Beneath the endocardium of the left ventricle there are three or four hemorrhagic spots 1 to 3 mm. wide, and extending 0.5 to 1 cm. along the crests of the muscular ridges. The heart is otherwise normal.

Lungs: Wt. 320 gm. Vol. 330 cc.

The lungs are voluminous but not extremely so. Pleura is smooth, but looks thick and slightly opaque (edematous), giving the suggestion of a film over the lung.

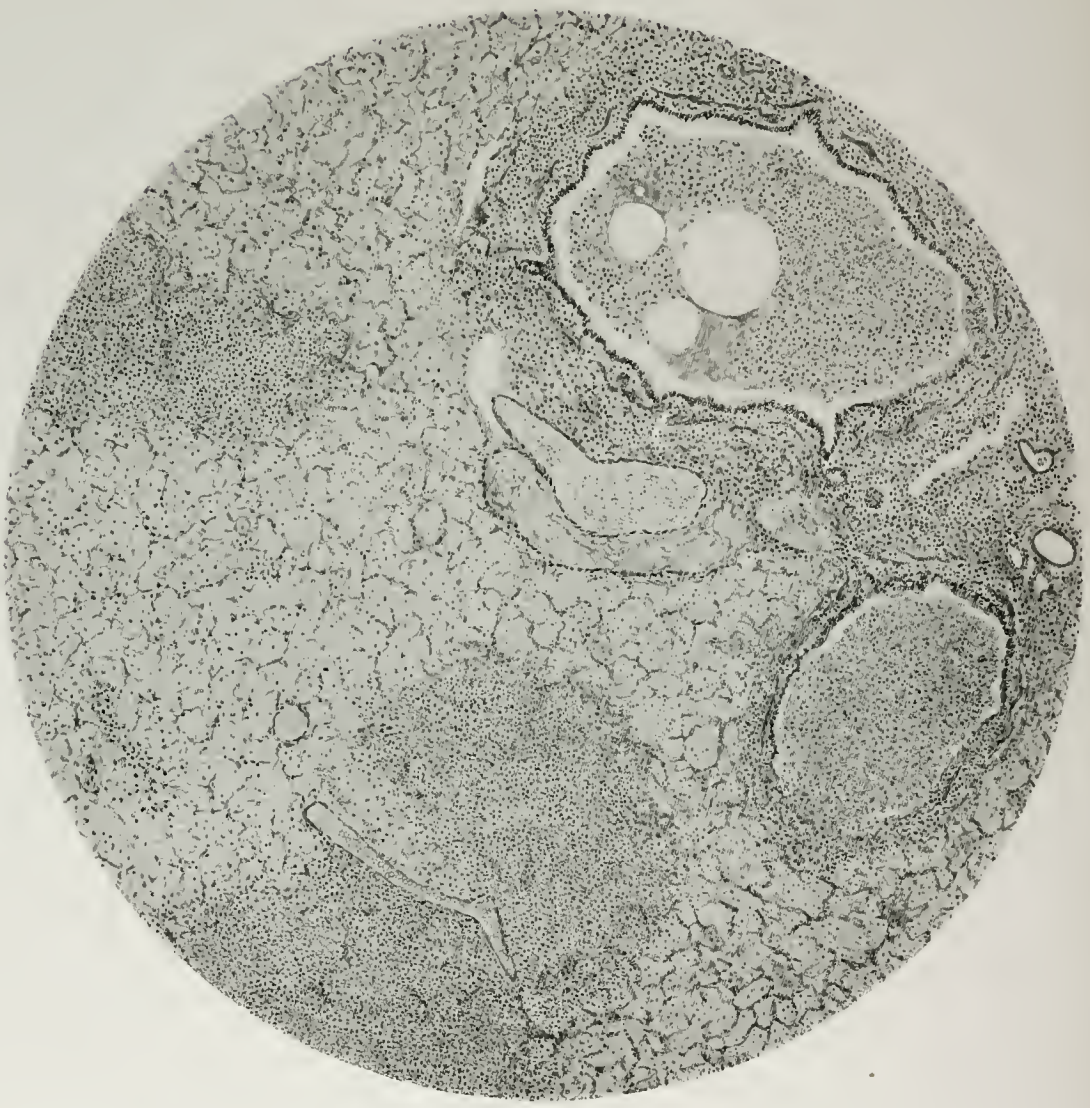

FIG. 4. EARLY STAGE OF BRONCHO-PNEUMONIA. 3 DAYS AFTER GASSING.

The lungs are unusually colored, being a dusky, bluish red or pink, distinctly cyanotic with a semi-translucent quality over all. Here and there are light, whitish patches, but these are neither large nor numerous (as in phosgene cases). In such patches there is crepitation, but practically everywhere else the lung is doughy and airless (Fig. 1).

On section, clear fluid and blood pour out like water from a squeezed sponge. The tissue is red and semi-translucent with occasional lighter, air-containing patches. Near the margins of the upper lobes, there are a few small emphysematous areas.

The bronchi, like the lung proper, are full of fluid, and in the large branches, there is some froth. The mucosa is somewhat reddened, and that of the smallest branches is rather opaque. About each there is a zone of edema, which is also conspicuous about the larger blood vessels.

The trachea is full of sticky froth. Its mucosa is slightly reddened but is otherwise normal.

The remaining organs,—liver, spleen, kidneys, adrenals, gastrointestinal tract, brain, —are negative.

Microscopic Findings: There is little worthy of note aside from the respiratory tract. The *tracheal* epithelium is practically everywhere intact, but in places the superficial cells are somewhat shrunken and distorted and have lost their cilia; a few are desquamated. In the largest bronchi a similar condition is seen, but as one passes downward into the medium-sized cartilage-containing tubes, the injury is far more serious. The superficial cells are quite necrotic, and the entire layer is partially loosened from the wall (Fig. 5). In the bronchioles and atria, there is not only death of the living cells but necrosis of the wall itself (Fig. 6).

The lung tissue shows practically everywhere a complete filling of the alveoli with coagulated edematous fluid, which is quite rich in albumin (Figs. 3 and 5). A few air bubbles are seen, but these are more prominent in the bronchial fluid. Desquamated alveolar cells are fairly numerous, and there is some fibrin free in the alveoli. Covering the septa everywhere, like vines on a lattice, are strands of fibrin.

Special fibrin stains show that the fibrin threads permeate the alveolar walls interrupting the capillary bed. As in the phosgene and chlorine cases, fibrin is most abundant in and about the walls of the bronchioles where the damage to the tissue is greatest.

SUMMARY

Extreme edema and congestion of lungs; necrosis of bronchial epithelium and bronchiolar walls; dilatation of heart; passive congestion of the abdominal viscera.

The findings in the case just described are quite typical of acute chlorpicrin death. There is little difference in the picture whether the animal dies four hours or twenty-four hours after gassing, except that in those living longer an early inflammatory reaction is generally found. More will be said of this in discussing the " delayed deaths."

There is in all of these early deaths an overwhelming edema of the lungs, which constitutes the most striking feature of the autopsy findings. The degree of edema, as judged by the lung-heart and lung-body weight ratios, varies considerably with individual animals (Table III), but the average for dogs dying in the first 6 hours, 6 to 12 hours or 12 to 18 hours after gassing is practically the same. This might suggest that death ensued in each case when a certain degree of edema was reached. But an analysis of the figures obtained from dogs which were apparently recovering, killed 18 to 48 hours after gassing, shows that

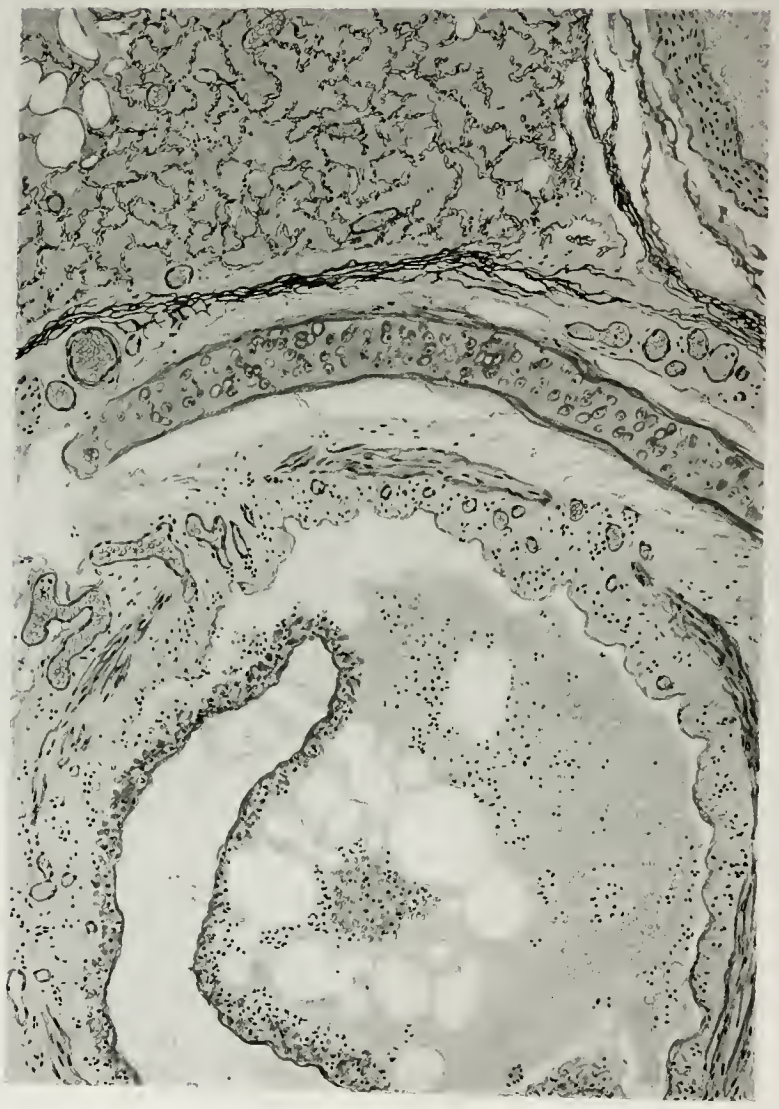

FIG. 5. NECROSIS OF BRONCHIAL EPITHELIUM AND EDEMA OF LUNGS IN ACUTE STAGE.

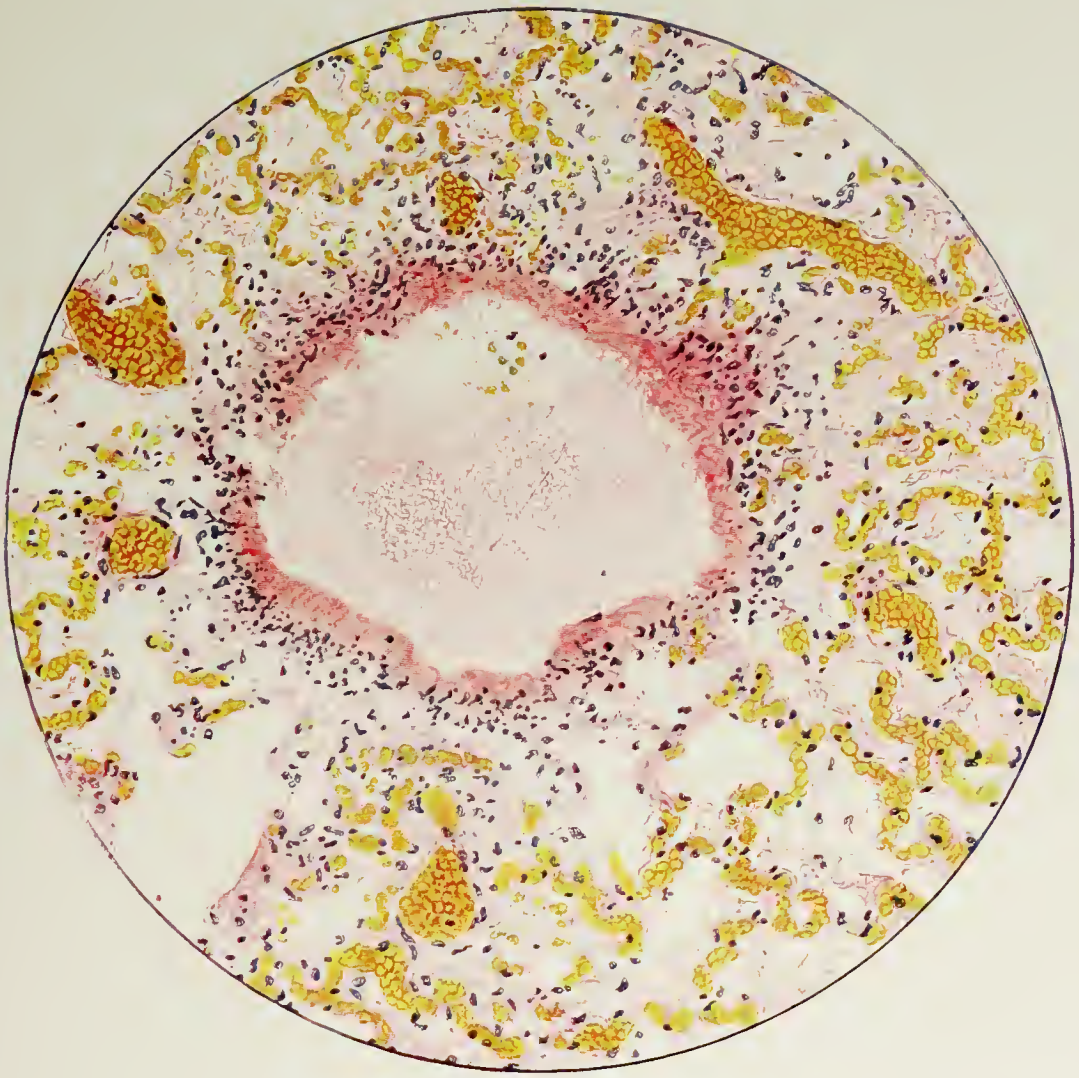

PLATE XV

FIG. 6. NECROSIS OF WALL OF BRONCHIOLE AND EXTREME CONGESTION, ACUTE STAGE.

among these the degree of edema, based on the proportionate weight of the lungs, heart, and body, was as great as in the animals that died. In other words, the presence of any particular quantity of fluid in the lung does not seem to be the cause of death. This idea has been substantiated experimentally by Winternitz and Smith (see p. 162).

What then is the cause of death?

There is evidence both clinically and anatomically of cardiac embarrassment:—dilatation of the right side of the heart, marked venous stasis, etc. The increased viscosity of the blood due to the loss of great quantities of serum by way of the lungs, emphasized by Underhill and others, no doubt puts a strain on the heart. But possibly more important than this is the accumulation of fibrin in the pulmonary septa, which forms a widespread barrier to the flow of blood through the lungs.

Several dogs dying from the 4th to the 7th day after gassing with little or no pneumonia showed evidence of extreme circulatory disturbances; examination of the lung in these cases revealed great quantities of old, unresolved fibrin throughout the pulmonary septa.

DEATH IN THE SUBACUTE OR CHRONIC PERIOD

The per cent. of animals dying on any one day after the first 48 hours is relatively small (see Chart I and Table I), but the total number of these "delayed deaths" is considerable in any large series of experiments. The cause of death is in almost every instance infection of the respiratory tract. This may begin within a few hours after gassing, but generally does not become widespread for several (two to four) days. In some instances the infection runs a chronic course, killing only after weeks or even months.

Dogs dying 2 to 10 days after gassing usually show a purulent bronchitis and bronchopneumonia (See Table II). Several lobes are almost always affected. Occasionally, patches of consolidation are found throughout the entire lung. The upper lobes are more often involved than the lower. This may be accounted for either by the greater dependency of the upper lobes in four-footed animals or by the poorer drainage due to the more abrupt branching of the bronchi. There is a greater tendency to abscess formation and extension of the infection to the pleura than after phosgene gassing. Organization of the pneumonic exudate occurs frequently.

It will not be necessary to go into the gross and microscopic findings in these cases, since the picture is practically the same as after chlorine and phosgene gassing, and is fully described in the separate papers on the pathology of these gases.

RECOVERED ANIMALS

Twenty-five animals which had survived exposure to a lethal concentration of chlorpicrin were killed at different periods after gassing (see Table I for detailed figures). These have shown very clearly the nature of the reparative processes which follow the gas injury.

The edema begins to regress after about two days, but at least a week is required for its complete disappearance.

It may be mentioned in this connection that the quantity of fluid present in the lungs in some of the two- and three-day dogs, in which all untoward symptoms had disappeared, was found to be as great as in the dogs which had died. There was, however, a greater quantity of residual air in the lungs, as shown by a comparison of the weights and volumes.

Fibrin in the alveolar spaces and walls is removed rather slowly, old strings and plugs of it being demonstrated sometimes seven or eight days after gassing.

FIG. 7. LUNG OF "RECOVERED" DOG KILLED 4 DAYS AFTER GASSING. IN ALVEOLI ABOUT BRONCHIOLES THERE ARE STRUCTURES RESEMBLING GIANT CELLS. THEY ENCLOSE OLD MASSES OF FIBRIN AND DEBRIS OF RED BLOOD CELLS.

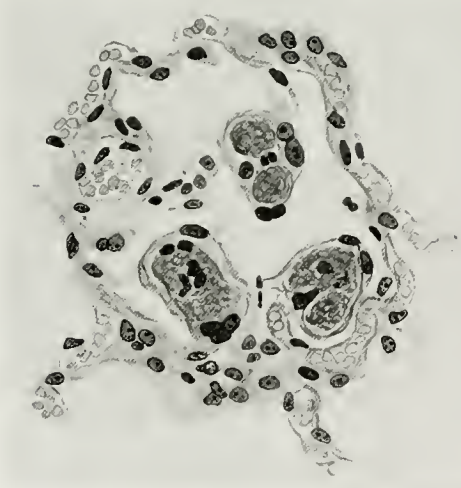

FIG. 8. HIGHER MAGNIFICATION OF FIELD IN FIG. 7, SHOWING STRUCTURE OF "GIANT CELLS." THE RESEMBLANCE TO CAPILLARIES IS QUITE STRIKING.

Where the bronchiolar walls have been seriously damaged, and this happens quite regularly after exposure to high concentrations, an active proliferation of fibroblasts begins about the dead area as early as three days after gassing, and the bronchial cavity is soon filled with granulation tissue. The final picture is that of an obliterative bronchiolitis, such as is well illustrated in the Chlorine and Phosgene papers.

Regeneration of the epithelium of the bronchi and alveoli proceeds fairly rapidly. It is best seen in dogs which have been exposed to a sub-lethal concentration of the gas, to kill only the superficial layer of cells.

In sub-lethal exposures, one sees also quite regularly curious structures in the alveolar spaces, which under low magnification, look like giant cells (Fig. 7). Under high power, they have the general structure of capillaries (Fig. 8), although one finds in all only disintegrated red blood cells and fibrin, no fresh blood. We were inclined at first to interpret these structures as foreign body cells, which were formed about masses of cell débris and fibrin, but a more careful study shows that they are attached to the alveolar wall and are probably sections of bulging capillary tufts which have become thrombosed.

COMPARISON OF THE PATHOLOGY OF CHLORPICRIN WITH THAT OF PHOSGENE AND CHLORINE.

Chlorine injures by combining directly with the cytoplasm of exposed cells, or through the formation of HCl, which in turn acts on the tissues. Phosgene, $COCl_2$, coming in contact with water, rapidly decomposes with the liberation of HCl, which constitutes the toxic agent. Chlorpicrin is very stable *in vitro*, and it has not yet been determined just how it reacts with tissues to injure them; but it seems likely that, as in the case of phosgene, its toxicity is referable to the chlorine part of its molecule, which is in some way split off as the gas reaches the tissue.

It would appear, therefore, that with each of the three gases, the directly injurious agent is the same,—chlorine,—and that their pathologic effects should be very similar. The description of the lesions produced in dogs by the three gases, as given in the preceding pages and in the separate papers on phosgene and chlorine, shows that this assumption is correct. There are, however, certain points of difference, which are sufficiently clear cut to enable an experienced observer to say from an examination of the organs of a gassed animal, which of the three gases has been used. Some of these points will be taken up in the succeeding paragraphs.

INJURY TO THE RESPIRATORY EPITHELIUM

Chlorine damages, and in high concentration entirely destroys, the epithelial lining of the upper portion of the respiratory tract,—trachea, large and medium sized bronchi. Although the injury may extend to the distal alveoli as well, causing focal areas of necrosis in the lung (Fig. 12, Chlorine paper) and desquamation of the alveolar epithelium, the most severe injury is suffered by the trachea and bronchi.

Phosgene, on the other hand, spares the trachea and larger bronchi, but destroys the epithelium of the smaller bronchi and bronchioles. Even the outer coats of the smallest air tubes show evidence of serious injury, and the alveolar walls are everywhere damaged, though rarely necrotized.

Chlorpicrin occupies an intermediary position in its action on the respiratory epithelium. The lining cells of the trachea and the very large bronchi are definitely injured in places, as

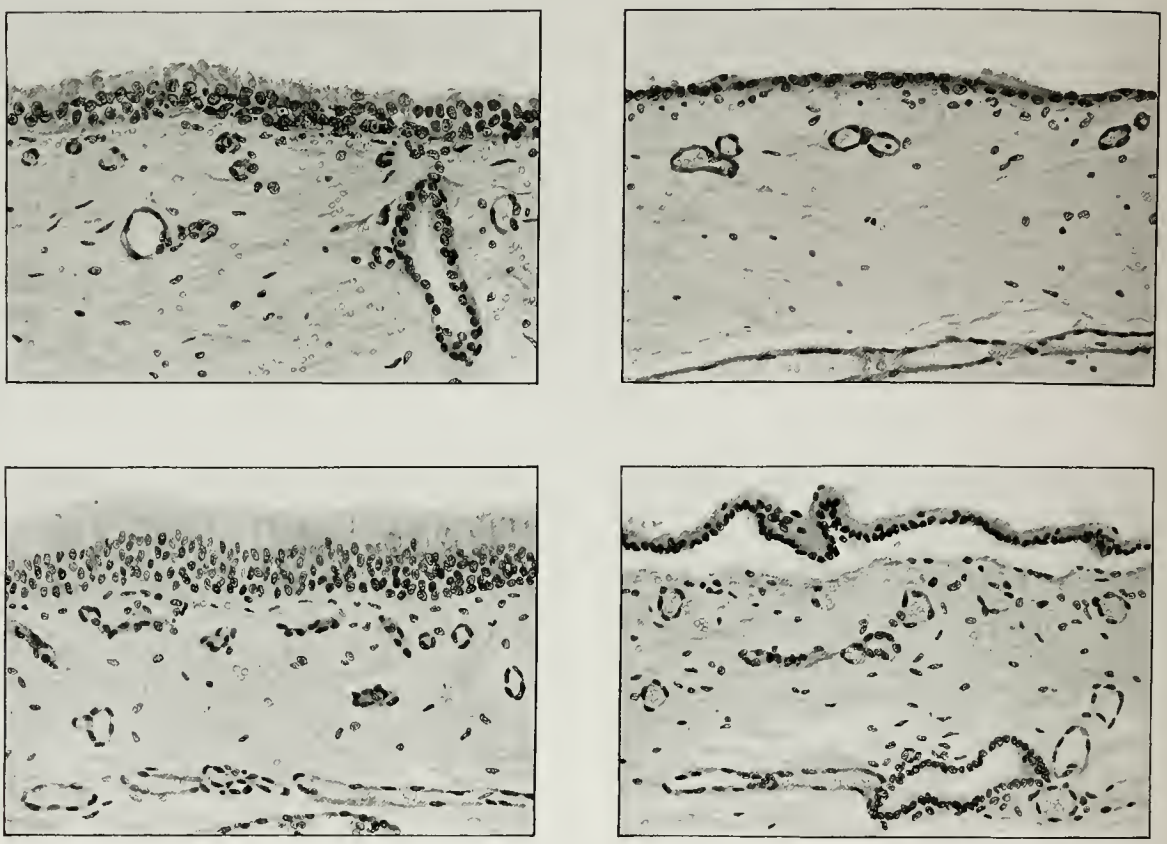

FIG. 9. A COMPARISON OF THE INJURY TO THE TRACHEAL MUCOSA BY CHLORPICRIN, PHOSGENE AND CHLORINE.

(A) AND (B)—CHLORPICRIN. (B) THE EPITHELIUM MAY BE INTACT, THOUGH DISTORTED, OR PARTIALLY EXFOLIATED.

(C)—PHOSGENE. MUCOSA IS PRACTICALLY UNDAMAGED.

(D)—CHLORINE. MUCOSA IS "COOKED" AND EXFOLIATED.

shown by irregularities in the ciliated surface or loss of cilia and occasional desquamation of the superficial layer of cells. But there is nowhere seen the rapid and complete coagulation of the entire mucous surface such as chlorine produces (see Fig. 4, Chlorine paper). The medium-sized and smaller bronchi, on the other hand, suffer very severe damage, which is even more marked than with phosgene. There is often complete disintegration of the walls of the bronchioles.

The changes in the alveolar walls are practically the same as after phosgene gassing.

This difference in the behavior of the three gases toward the several portions of the respiratory tract is not easily explained, but must be related in some way to the fact that chlorine requires no preliminary decomposition for its action, thus hitting hardest the first tissues with which it comes in contact; whereas phosgene and probably chlorpicrin also, must be first broken up, a process which may take place in the moist air of the smaller bronchi or in the cytoplasm of the lining epithelium while being absorbed, or, as Hoover has suggested in the case of phosgene, only after absorption. The place and rate of absorption and decomposition would thus determine the site and degree of injury.

Edema, Congestion, and Emphysema: Each of the three gases produces a high grade of edema of the lungs, which develops with great rapidity after exposure. Its development is more rapid with chlorine and chlorpicrin than with phosgene, where corresponding toxic concentrations are used. In the two former a maximum degree of edema is reached in less than 12 hours; whereas after phosgene the peak is reached in about 18 hours. But the time varies greatly with individual animals.

The actual quantity of fluid poured out into the lungs, as judged by the lung-heart and lung-body ratios, is slightly greater with phosgene than with chlorpicrin, although in the latter, the fluid fills the lungs more completely (we have no figures for chlorine). This point will be taken up again in connection with the volume of the lungs. In both chlorine and chlorpicrin gassing, there is a very striking edema of the mediastinal tissues and the pleura; this is not as conspicuous with phosgene.

Congestion of the lungs, although present in all, is much more pronounced with phosgene than with the other two gases, and constitutes one of the distinguishing gross features. Phosgene lungs are almost regularly dark bluish red or purple with whitish emphysematous patches; chlorpicrin lungs on the other hand are, as a rule, lighter in color, the basic hue being a bluish pink.

Patches of acute emphysema are common to all, but phosgene easily stands first in the number and extent of the acutely distended foci of lung tissue. A comparison of the illustrations of gross lesions will emphasize the differences. Figures on the weights and volume of chlorpicrin and phosgene lungs supply more exact data on this point.

In 18 phosgene dogs dying within 24 hours after gassing, the average volume of the lungs was 579 cc., wt. 459 gm. In 30 chlorpicrin animals, the figures were 413 cc. and 353 gm. The average weight of the dogs in the two series was approximately the same, 12 kilos. Phosgene lungs are seen to be greater both in volume and weight, but the difference between the average weight and volume, which represents roughly the amount of residual air confined chiefly in emphysematous patches, is 129 in the phosgene series, while in the chlorpicrin series it is less than half this amount (see Table III for chlorpicrin figures). The contrast in the gross appearance of the lungs is often much more striking than these figures would suggest. In many instances the chlorpicrin lungs are uniformly doughy and airless, and the figures of the weight and volume are practically the same, or differ by only 10 to 25 points. We have observed with phosgene no such close approximation of the weight

and volume, the smallest difference noted being 50, and this was in a small dog, weighing only 5.5. kilos, where the volume of the lung was 325 cc. and weight, 275 gms.

RESPIRATORY INFECTION AND CHRONIC CHANGES IN THE LUNGS

An inflammatory reaction is seen in the lungs of almost every animal that dies more than 24 hours after gassing with chlorine, phosgene, or chlorpicrin, and in a large proportion of those dying earlier. In this particular, there is practically no difference in the three gases. But the per cent. of animals which succumb to the infection after passing through the acute edema stage appears to be somewhat higher with chlorine than with the other two gases. The secondary rise in the death curve (see Chart I, chlorine paper) shows this to be so. In view of the greater injury to the trachea and bronchi produced by chlorine, which allows not only the freer entry of pathogenic bacteria into the lungs but also leads to a necrotizing tracheitis and bronchitis as well, the particularly large number of delayed deaths from infection is not surprising. As might be expected, chlorpicrin comes second to chlorine in producing a condition favorable to infection. Indeed, in the matter of infections of the pleural cavity,—fibrinous pleurisy, and empyema,—it has appeared to stand first, but the series of cases is small, and the percentages are therefore less conclusive.

The late changes in the lungs, that is, the lesions found in animals which have died or have been killed ten days to several months after gassing, are practically the same for all three gases: focal emphysema and atelectasis, chronic bronchitis, generally of the obliterative type, and occasional examples of bronchiectasis. An active chronic infection in and about the bronchi, with patches of organizing pneumonia, is seen not infrequently. On the whole, these chronic changes are most pronounced after chlorine gassing, but the character of the lesions is the same in all, and similar pictures have been described for other gases of the respiratory irritant group.

In other words, it is only in the acute period that it is possible to distinguish between the effects of these gases, and even then it can be done only by an experienced observer who is familiar with the variations in the lesions produced by each gas.

SUMMARY

Chlorpicrin, like chlorine and some of the other gases of the respiratory irritant group, injures the epithelium of the entire respiratory tract, but all portions of the tract are not equally affected. The trachea and largest bronchi, though irritated, suffer only slight and transient injury. The medium sized and small bronchi are most affected. There is a uniform, widespread damage of the alveolar walls, which, however, is not severe enough to lead to necrosis. The alveoli are apparently nowhere protected by constriction of the bronchi.

An overwhelming edema of the lungs rapidly follows exposure to a lethal concentration of the gas. In extreme cases practically every alveolus is filled with fluid, so that at autopsy the weight and volume of the lungs (expressed in grams and cubic centemeters) approximate one another. In addition to the fluid in the lung itself, there is also marked edema of the mediastinal tissues and pleura, which is even more striking than in phosgene and chlorine gassing. The edema fluid contains fibrin in places, and a great deal of fibrin is found in the alveolar walls. It is especially abundant in cases that have succumbed after twenty-four hours.

Partial or complete occlusion of the smaller bronchi by inflammatory exudate or masses of necrotic cells leads to focal emphysema or atelectasis, but this is not such a

striking feature at autopsy as in death from some of the other respiratory irritant gases (phosgene, diphosgene).

Infection of the lungs, with the development of a widespread bronchitis and bronchopneumonia, is seen in a large percentage of those animals which do not die in the first few hours after gassing. Abscess formation, pleurisy, fibrinous or purulent, and organizing pneumonia are common complications. In recovered animals there is a regeneration of the epithelium of the bronchi and alveoli; and organization of the necrotic bronchiolar wall, with scar formation (obliterative bronchiolitis). Focal atelectatic and emphysematous patches remain as permanent gross evidences of the gas injury.

A study of "recovering" animals killed at different periods indicates that the cause of death in the early stage, that is, before infection becomes well established, is not due to the edema *per se* but probably to obstruction of the blood flow through the lungs caused by extensive deposition of fibrin in the alveolar walls. The increased viscosity of the blood from the loss of fluid into the lungs, emphasized by Underhill, is no doubt also a very important factor. Likewise some of the "delayed deaths" are to be attributed to this "fibrinous obstruction" of the pulmonary circulation, but the great majority are obviously due to an infection of the lungs, bronchi, or pleura.

A comparative study of the pathology of chlorpicrin, chlorine, and phosgene shows that chlorpicrin in its action on the respiratory tract, occupies an intermediate position between chlorine and phosgene. It damages the trachea and larger bronchi less than chlorine but more than phosgene. In its action on the bronchioles and alveoli, it resembles phosgene very closely, but in several other respects the lesions are more like those of chlorine. The gross and microscopic differences in the acute effects of the three gases on dogs are sufficiently clear to enable an experienced observer to determine by autopsy which gas has been used. It should be possible to make practical application of this knowledge on the battlefield in the identification of the gas being used by the enemy.

TABLE I

Time of death after gassing	*Died*	*Killed*	*Total*
1st 12 hours	38	1	39
12 to 24 "	19	4	23
2nd day	15	2	17
3rd "	9	0	9
4th "	1	8	9
5th to 10th day	2	2	4
11th to 26th "	8	8	16
	92	25	117

TABLE II

	Per cent. showing pneumonia.
Dogs dying 1st 12 hours	27
" " 12 to 24 "	45
" " 2nd day	60
" " 3rd "	63
" " 4th "	100
" " 5th to 10th day	100
" " 11th to 26th "	71

TABLE III

							Lung			
No.	*Breed*	*Sex*	*Concen.*	*Death, hrs. after gassing*	*Body weight*	*Heart weight*	*Volume*	*Weight*	*Differ.*	*Wt. Index*
1	Cur	M	1.039	4	10,400	76	415	400	15	4.04
2	Collie	M	.985	6	11,800	120	635	465	70	2.98
3	Bull	M	1.070	13	10,400	80	450	375	75	3.60
4	Cur	M	.992	12	13,600	125	400	335	65	2.06
5	Cur	M	.930	5	19,500	175	510	510	0	2.26
6	Collie	M	.891	8	13,400	95	375	355	20	2.87
7	Mongrel	F	.906	8	9,300	90	300	245	55	2.09
8	Cur	M	.819	7	900	105	360	320	40	2.34
9	Collie	M	.985	12–24	11,350	105	425	350	75	2.56
10	Collie	M	1.107	12–24	15,900	100	400	350	50	2.69
11	Cur	M	1.029	12–24	9,800	105	350	300	50	2.19
12	Collie	M	1.075	12–24	15,400	140	500	450	50	2.47
13	Cur	F	1.015	12–24	10,400	80	310	300	10	2.88
14	Cur	M	.991	9	10,400		390	350	40	
15	Coach dog	F	1.034	4	9,000	65	420	345	75	4.07
16	Cur	M	1.064	8	8,340	95	300	225	75	1.81
17	Cur	F	1.017	9	7,000	62	290	225	65	2.79
18	Cur	M	1.006	7	8,100	75	325	290	35	2.97
19	Airedale	F	.911	12–24	13,160	150	575	525	50	2.70
20	Cur	M	.983	5	7,000	60	300	225	75	2.88
21	Mongrel	M	.890	12–24	7,900	75	350	250	100	2.56
22	Cur	F	.999	12–18	8,500	75	300	275	25	2.81
23	Cur	M	1.020	8	8,800	75	300	275	25	3.79
24	Cur	M	1.041	12–18	9,300	96	400	350	50	2.79
25	Airedale	M	1.015	10	9,300	127	280	250	30	1.51
26	Poodle	M	1.087	7	8,200	84	225	205	20	1.87
27	Cur	M	1.046	8	12,900	130	375	365	10	2.16
28	Collie	M	.891	26	16,000	125	480	300	180	1.85
29	Collie	M	.752	20	18,000	151	480	410	70	2.04
30	Cur	M	.908	8	10,000	102	310	280	30	2.12

Table III.—Data indicating the degree of edema of lungs and acute emphysema in dogs *dying* acutely after chlorpicrin gassing. The extent of the edema may be judged by the weight index in the last column. Index is obtained by dividing the lung weight by the heart weight, and this quotient by 1.30, the normal proportion. The weight index thus represents the degree of increase in lung weight. The great variation in the figures 1.51 to 4.07 is significant (see text). The slight differences in the weight and volume of the lungs show the small amount of emphysema present as compared with phosgene and superpalite.

NOTE ON THE COMPARATIVE PATHOLOGY OF CHLORPICRIN POISONING

BY

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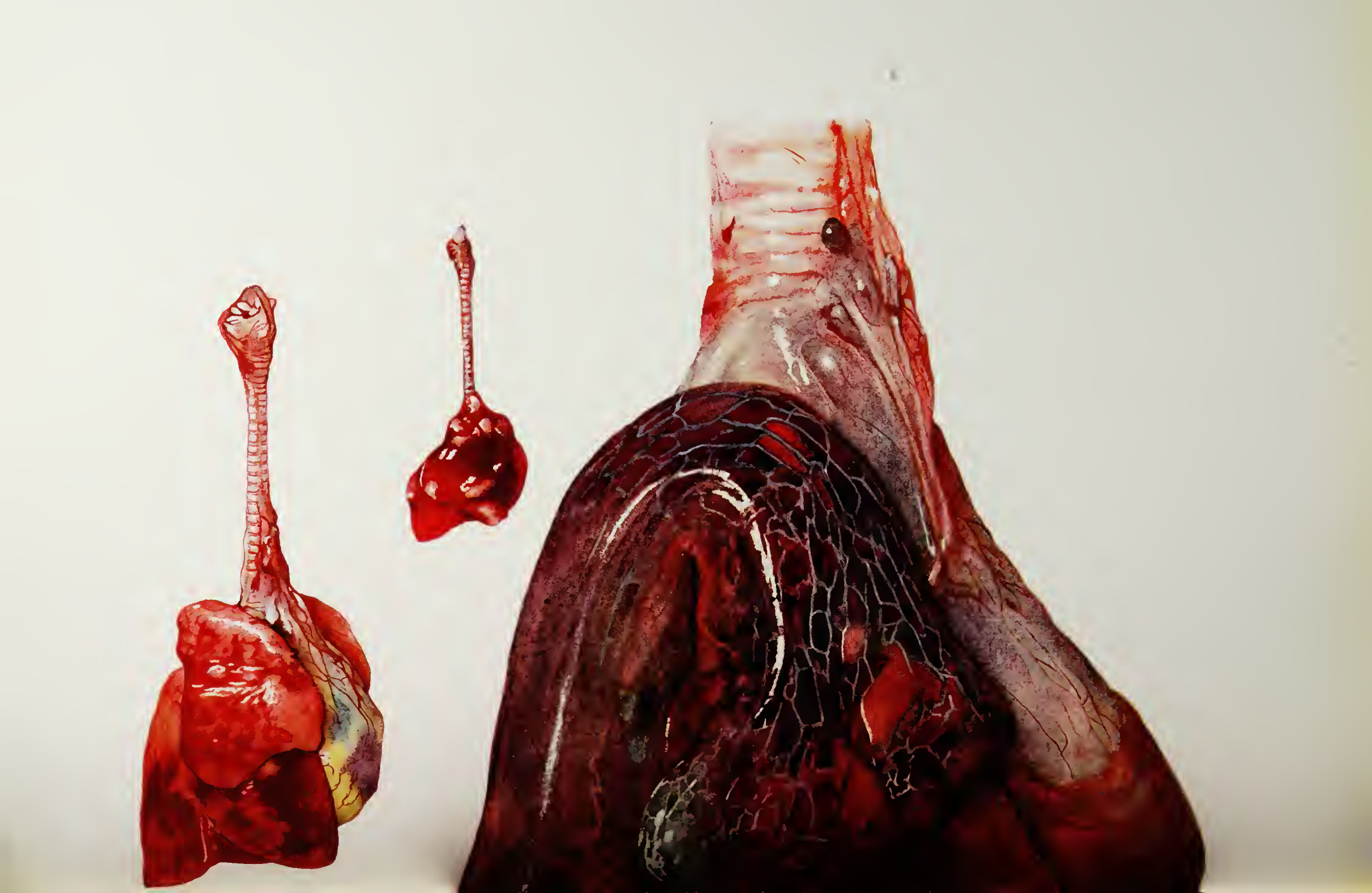

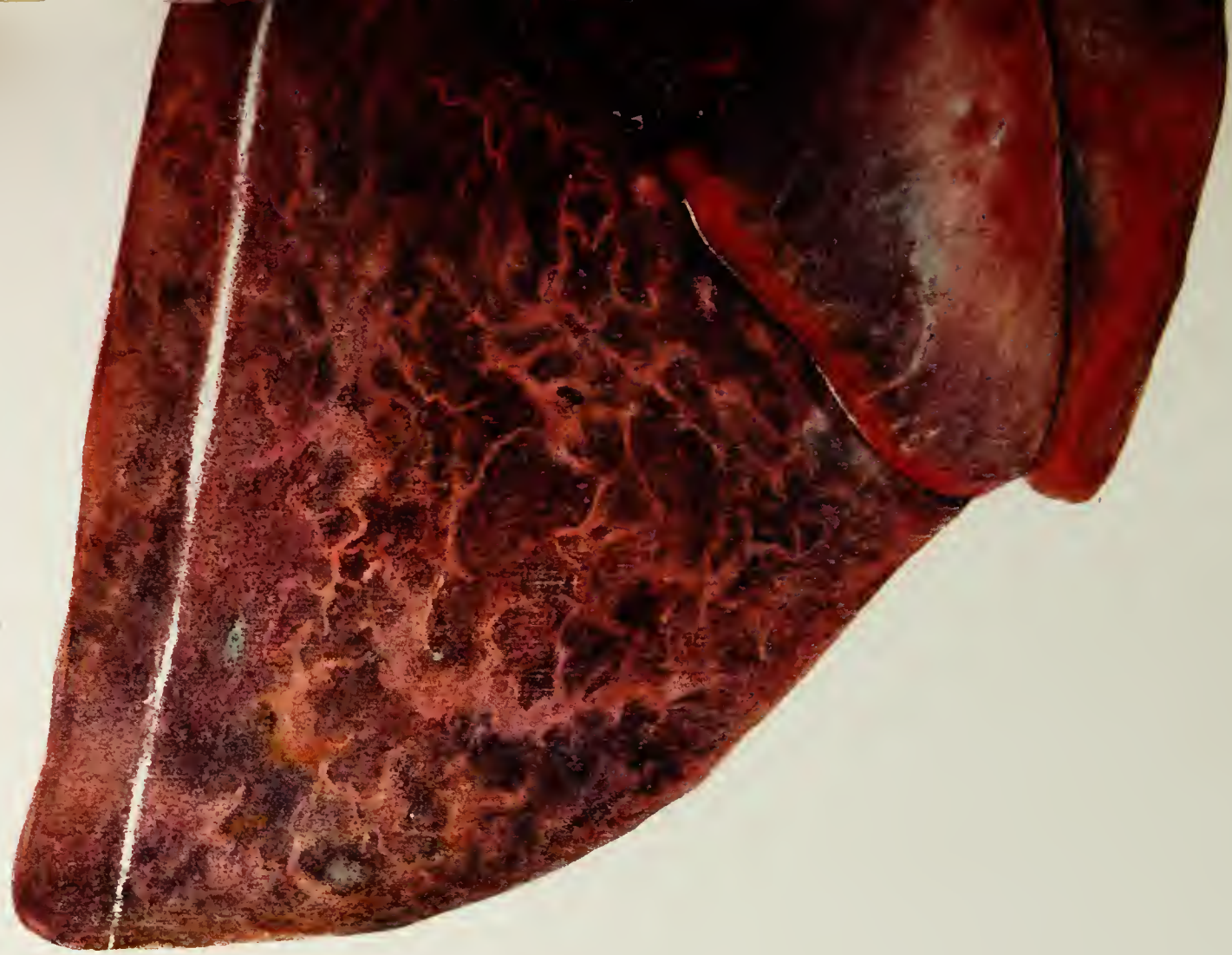

PLATE XVI

FIG. 1: LUNGS OF GOAT, MONKEY, AND RAT SURVIVING, RESPECTIVELY, 4 HOURS AND 10 MINUTES, 4 HOURS AND 55 MINUTES, AND 6 HOURS, AFTER EXPOSURE FOR 15 MINUTES TO CHLORPICRIN.

NOTE ON THE COMPARATIVE PATHOLOGY OF CHLORPICRIN POISONING

The only available data upon the toxicity of chlorpicrin for different species of animals is presented by a British report summarized in a note by Captain E. K. Marshall, Jr., March 5, 1918.

Marshall tabulates the lethal concentration for chlorpicrin gas at 3-, 15-, and 30-minute intervals for a number of different animals.

TABLE

Time	*3 min.*	*15 min.*	*30 min.*	
Rabbit	7.4	3.7	—	
Dog	"	1.5	0.74	mgm. per liter
Cat	"	—	0.37	
Monkey	"	1.5	—	
Goat	"	1.0	0.5	
Rat	"	1.0	0.5	
Guinea pig	"	—	—	

While these figures are only suggestive, it seems that the variation in susceptibility increases with the lethal concentration for longer time intervals. No confirmatory reports are at hand, and it has been impossible to find any studies on the comparative pathology of chlorpicrin.

Three experiments have been conducted in each of which a single animal of each of the above species was exposed in the same chamber to a concentration of 2.34 mgm. per liter of chlorpicrin for 15 min. A single observation characteristic of the three may be advantageously presented.

Species	*Survived*
Dog	40 min.
Mouse	2 hours
Goat	4 " 10 min.
Monkey	4 " 55 "
Rabbit	6 "
Guinea pig	6 "
Rat	6 "

These experiments were not carried out to determine toxicity but to obtain tissue for the comparative pathology. That the gross lesions are very similar is indicated by the accompanying illustration. It will be unnecessary to enter here into the pathology, as it has been found to be quite similar to that given in detail in the preceding paper on the changes produced by chlorpicrin in the dog.

THE PATHOLOGY OF SUPERPALITE POISONING

BY

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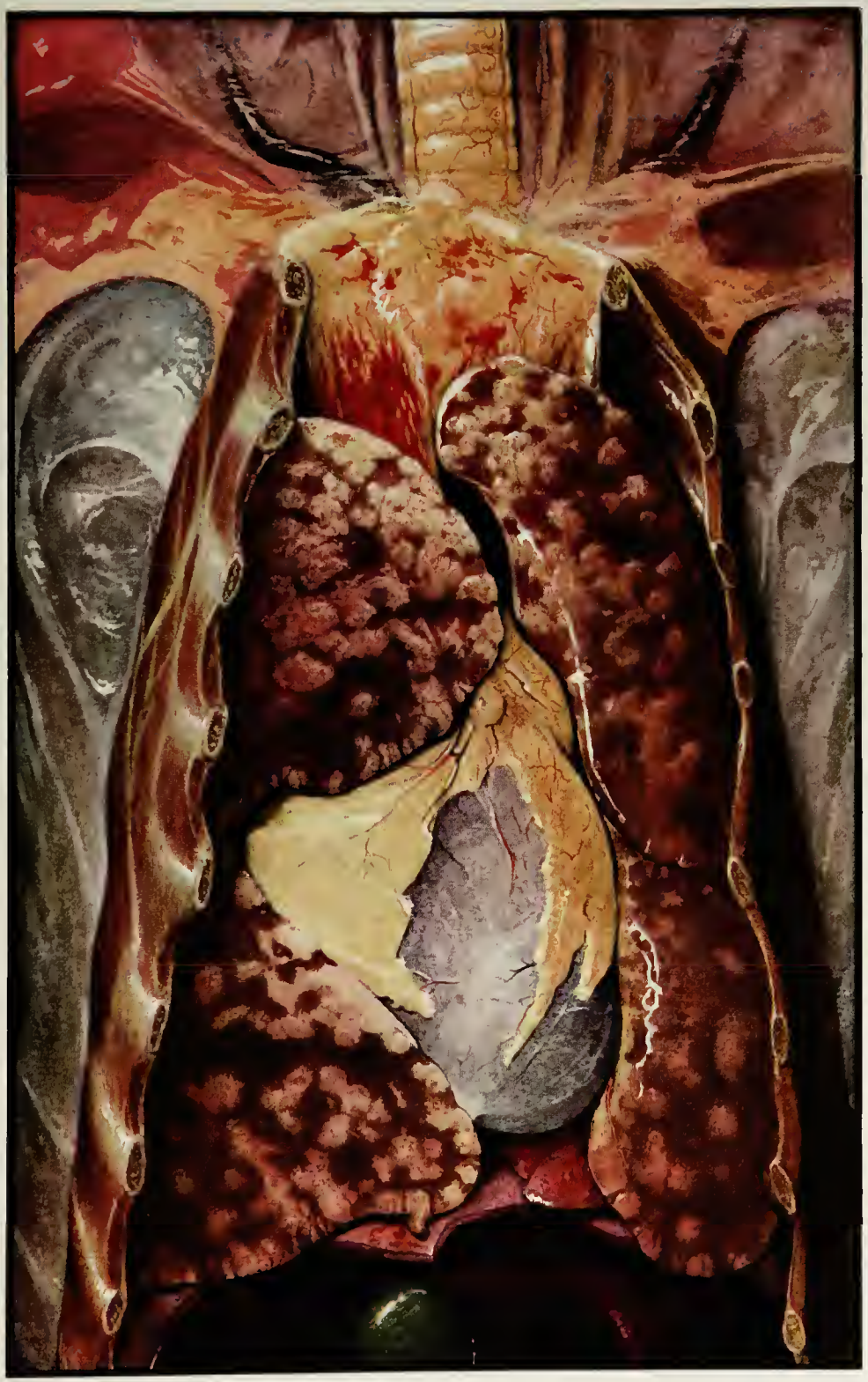

PLATE XVII

FIG. 1: THORACIC ORGANS *IN SITU* OF A DOG SURVIVING 24 HOURS AFTER A LETHAL DOSE OF SUPERPALITE. LUNGS ARE VOLUMINOUS WITH NUMEROUS SHARPLY DEFINED PATCHES OF ACUTE EMPHYSEMA.

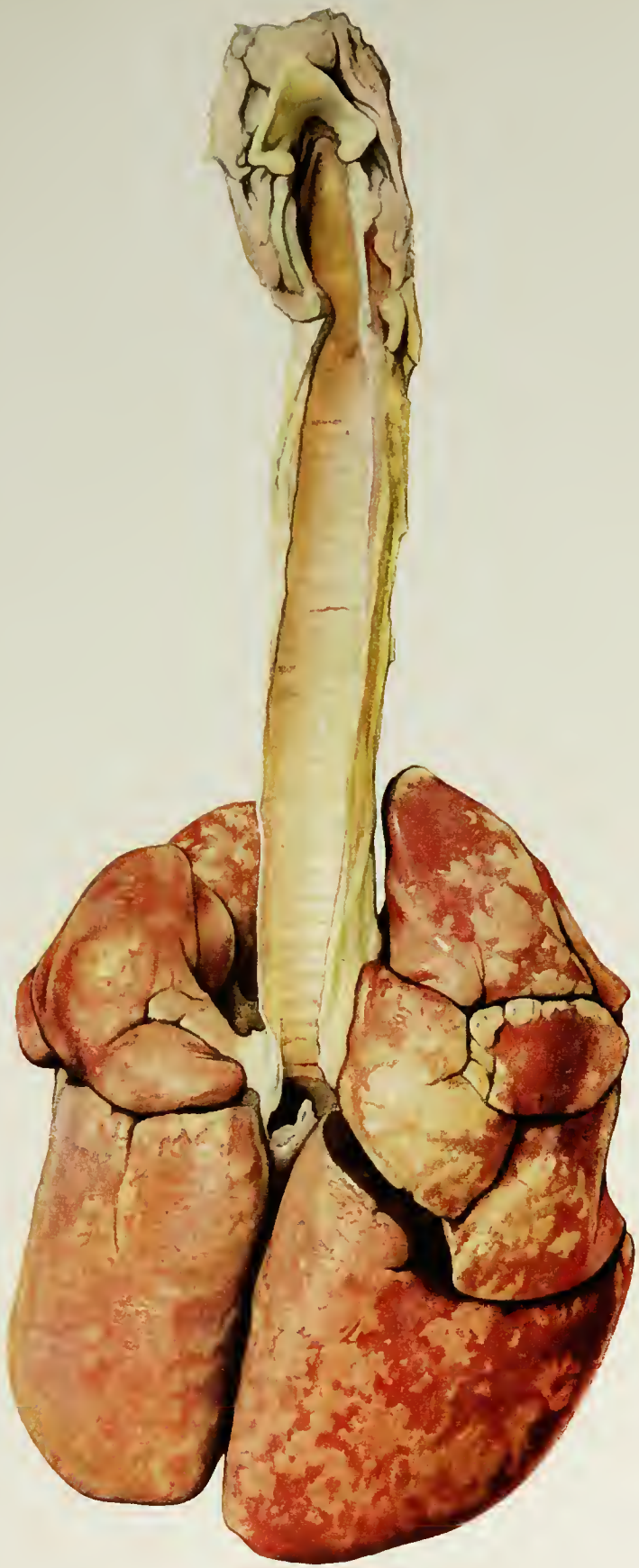

PLATE XVIII

FIG. 2: LUNGS AND TRACHEA OF DOG DYING 2 DAYS AFTER EXPOSURE TO SUPERPALITE. THE LEFT UPPER AND RIGHT MIDDLE LOBES ARE HEAVY AND FIRM SHOWING CONGESTION AND SOME ATELECTASIS. THE LEFT LOWER LOBE IS PUFFY AND EMPHYSEMATOUS; THE OTHER LOBES ARE OF MIXED CHARACTER AND HAVE SOME EDEMA. THE TRACHEA IS LINED BY A SMOOTH NORMAL LOOKING MUCOSA.

THE PATHOLOGY OF SUPERPALITE POISONING TRICHLOROMETHYL CHLOROFORMATE

("Diphosgene," "Superpalite")

INTRODUCTION

A NUMBER of substances related to phosgene were found in German shells during the later part of 1916 and all of 1917. Palite or chloromethyl chloroformate ($ClCOOCH_3Cl$) and superpalite, trichloromethyl chloroformate, or diphosgene ($ClCOOCCl_3$) are the most important of these compounds and are the ones which have been most extensively used by the Germans. The British and French have not employed these substances for military usage because of the difficulty of their manufacture and because they were regarded as possessing no advantage over phosgene.

In actual practice, superpalite has superseded palite, and palite is rarely found in the shells at the present time, except as it occurs as a by-product in the manufacture of superpalite.

Lately, reports seem to indicate that the use of superpalite by the enemy is decreasing. This is probably due to its high content of chlorine and, therefore, its high cost.

THE PATHOLOGY OF SUPERPALITE

The results included in the following report are based upon the gross anatomical and histological findings in 35 dogs. For convenience in describing the pathology of this gas, the material may be divided into three groups:

GROUP I. *Animals which succumb to lethal doses of the gas within 1 to 3 days after exposure (21 dogs).*

GROUP II. *Animals which die or are sacrificed 3 to 14 days after exposure (9 dogs).*

GROUP III. *Animals which survive longer than 2 weeks and are sacrificed up to 3 months (5 dogs).*

GROUP I. *Animals Which Succumb to Lethal Doses of the Gas Within 1 to 3 Days After Exposure.*

The action of the gas upon the tissues appears to be slow in onset, for no deaths occurred earlier than 8 hours after exposure, although the concentrations in many instances were relatively high. It is seldom that a dog dies within 8 to 12 hours; in fact, the majority of the gassed animals have not succumbed until the end of the first or second day. In the entire series, no death in the chamber or immediately after removal has resulted.

The *symptomatology* presents nothing unusual. During exposure, lachrymation and a

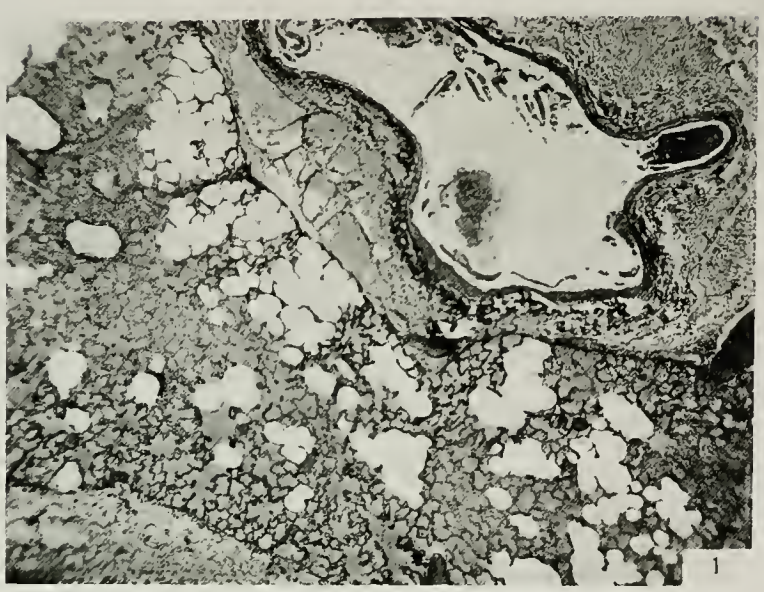

FIG. 3. SECTION OF LUNG SHOWING EDEMA IN ACUTE STAGE IN A DOG DYING 8½ HOURS AFTER EXPOSURE.

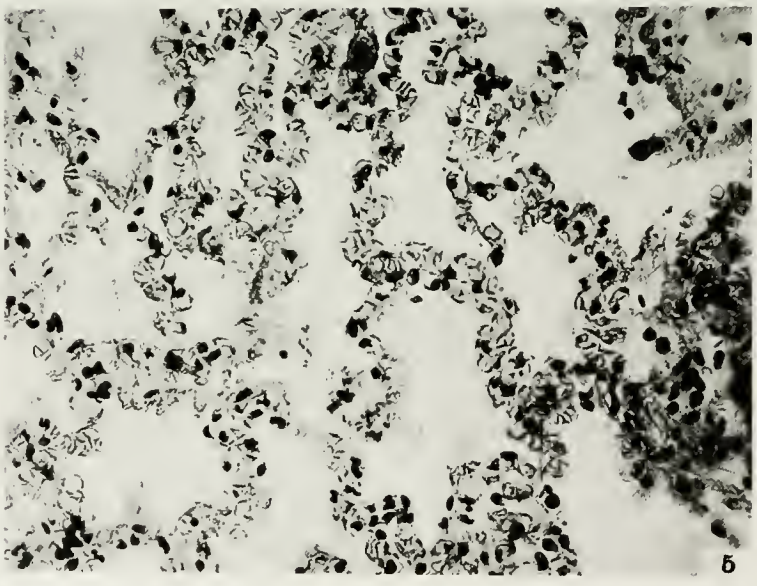

FIG. 4. HIGHER MAGNIFICATION OF SECTION OF LUNG, ACUTE STAGE, SHOWING ENGORGEMENT OF CAPILLARIES IN THE ALVEOLAR WALLS.

markedly increased nasal and salivary secretion is noted. After removal from the chamber, the animal becomes depressed; pulse and respiration may remain the same or rise slightly; the temperature remains unaltered. Twitching of the muscles or convulsions have never been observed, and the animals are always conscious till death. Vomiting and diarrhea are only rarely observed. (Abstract from clinical records.)

Externally, the animals which have died of acute poisoning present nothing striking. The conjunctivæ may be slightly hyperemic. There is always a profuse sero-sanguinous discharge from the mouth and nostrils. The buccal mucous membranes may be diffusely reddened.

The peritoneal cavity contains no excess of fluid, and its surfaces appear normal. The liver is usually large, deep red and firm, and extends far down into the peritoneal cavity. On section, the entire splanchnic area is found engorged. The spleen is purple, large, and succulent. The splenic pulp is found to be very abundant, while the Malpighian bodies are only indistinctly visible.

On opening the thorax, the pleural cavities are found to be almost obliterated by the voluminous lungs (Figs. 1 and 2). The pleural spaces, as a rule, contain no fluid, and their surfaces are moist, smooth, and glistening. The pericardial cavity is normal. The heart shows nothing unusual beyond a slight dilatation of the right ventricle.

The lungs are voluminous and completely fill the pleural spaces. The lobes of the right and left lung almost meet in the midline. They present a constant and characteristic picture. Alternating areas of pinkish gray emphysema and reddish brown atelectasis give the lung surface a strikingly mottled appearance. The pale areas may be diffuse or circumscribed. They are slightly raised and have a silvery luster, and when carefully examined are seen to be composed of groups of distended air-containing lobules. The dark areas are depressed, and on close inspection show no special architecture.

On sectioning the lungs, a profuse sero-sanguinous fluid drips from the cut surface. On pressure, the lung tissue pits and the escape of fluid is augmented.

The larynx, trachea, and bronchi are smooth and pale pink and contain a profuse, frothy, serous fluid. In some instances a considerable degree of hyperemia of the mucous membranes is found. A striking feature in these animals is the fact that the upper respiratory passages always remain normal, as in phosgene, and never exhibit edema or pseudomembranes, conditions so commonly met with in dogs suffering from the effects of other gases, such as chlorine or mustard.

Microscopically, the lungs are of great interest. Under low power, two characteristic conditions are discernible. First, areas in which the alveoli are distended, their walls thin and membraneous and the capillaries almost obliterated (Fig. 3). Second, areas in which the alveoli are compressed and in places entirely obliterated, with prominent alveolar walls in which the capillaries are tortuous and tightly packed with red blood corpuscles (Fig. 4).

Many of the alveoli contain a homogeneous pink-staining exudate, while others exhibit a fine, delicate network of fibrin (Fig. 5). The homogeneous precipitate is always most marked around the dilated termination of the bronchioles. The alveolar epithelium is to some extent desquamated and lies entangled in the fibrin threads. In other places escape of red blood cells has occurred so abundantly that the alveoli are almost filled by them.

The bronchioles appear in part dilated and in part in a condition of spasm, as indicated by a thin narrow lumen and by the knot-like muscle bundles, which stand out prominently in their corrugated walls. The lumen of the bronchioles may contain desquamated epithelium, fibrin, and red blood cells; and in the smaller bronchi, the epithelium, in many instances

FIG. 5. SECTION OF LUNG, ACUTE STAGE, SHOWING EXTREME EDEMA.

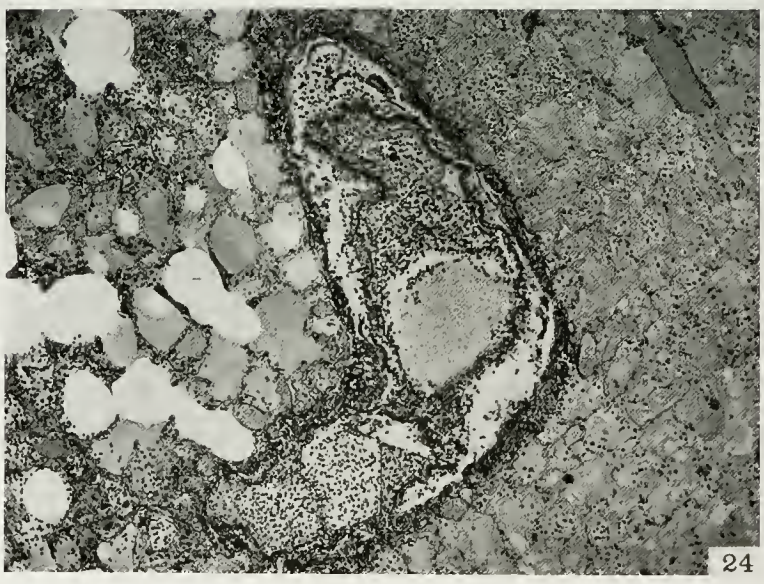

FIG. 6. SECTION OF LUNG SHOWING EARLY INFILTRATION OF THE ALVEOLI AND BRONCHI BY POLYMORPHONUCLEAR LEUCOCYTES; DOG DYING 8½ HOURS AFTER EXPOSURE.

may be elevated from the submucous surfaces by edema. Occasionally, the epithelium is separated entirely and lies as a pink-staining, structureless membrane, free within the lumen of the bronchiole.

Polynuclear leucocytes in relatively large numbers are found in the exudate of the bronchiolar lumina and also infiltrating their walls (Fig. 6). They grow less and less numerous but occur in small numbers in the alveoli that immediately surround the bronchioles.

The blood vessels of the lungs are prominent and are surrounded by an intense perivascular edema (Fig. 7). The lymphatics are everywhere distended and are very easily discernible on the surface of the lung and near the hilus as large, tortuous, fluid-containing channels.

SUMMARY

Superpalite in lethal concentration causes an intense irritation of the bronchioles and pulmonary parenchyma. Tremendous congestion and edema occur quickly. The bronchioles may be irregularly constricted, the ducti alveolares dilated, and the lung alveoli emphysematous or atelectatic. The epithelium of the bronchioles is necrotic and is found entangled in the inflammatory exudate of the lumina. The blood vessels of the alveolar walls are engorged, the alveolar epithelium is in part desquamated, and the alveoli contain large amounts of serum, fibrin, and leucocytes, particularly around the bronchioles. The upper part of the respiratory tract is practically unaffected.

GROUP II. *Animals Which Die or Are Sacrificed 3 to 14 Days After Exposure.*

The lungs in the gross after the first week show a marked diminution in the extent of the emphysema and atelectasis. Many of the emphysematous areas have entirely disappeared, and the purple of the atelectatic patches has faded (Fig. 8). On opening the thorax, the lungs are not nearly as voluminous as they were in animals dying soon after exposure to the gas. On section, they are somewhat more moist than normal and only slightly congested. A few scattered wedge-shaped, atelectatic areas persist, and there may be a broncho-pneumonic process involving portions of several lobes. The larynx, trachea, and bronchi have lost whatever congestion and hyperemia they may have exhibited during the first few days, and they now appear perfectly white, smooth and glistening, and normal in every respect. A few of the small bronchi which are associated with patches of pneumonic consolidation may contain muco-purulent material.

Histologically, the broncho-pneumonic areas show alveoli infiltrated with polymorphonuclear leucocytes and mononuclear cells. In all instances the alveolar walls have remained intact and their nuclei stain well. In no instance, has an abscess been encountered. The broncho-pneumonic exudate in the alveoli may present itself as hyaline balls (Fig. 9), which may be continuous with masses of similar material in the bronchioles. Organization of such masses has already been inaugurated. Elsewhere in the lung, one encounters mild grades of emphysema and persistent atelectasis. The perivascular edema and congestion of the alveolar walls have almost entirely disappeared. Many of the bronchioles exhibit desquamated epithelium, and in some of them sheets of dead epithelium mixed with mucus and leucocytes are seen in the lumina. The bronchi and trachea show an entirely normal picture. The epithelium is everywhere intact and normal in appearance. The other organs show nothing abnormal, grossly or histologically.

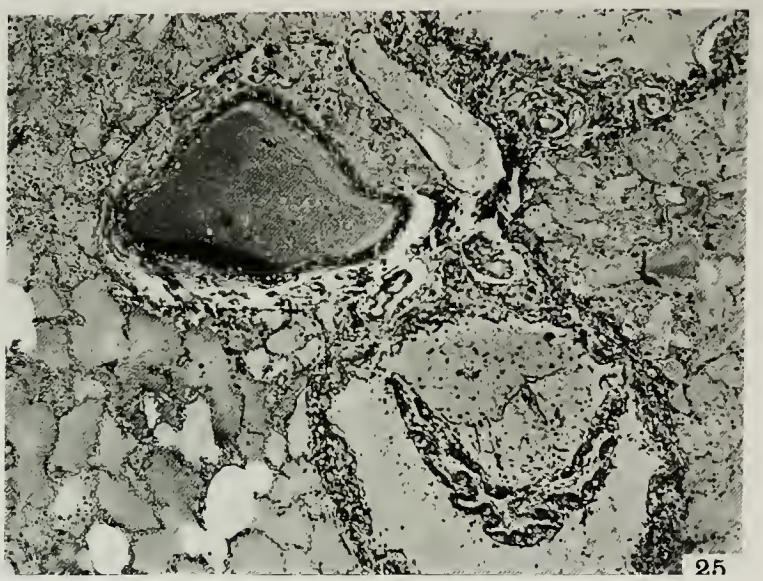

FIG. 7. HIGHER MAGNIFICATION OF FIG. 6.

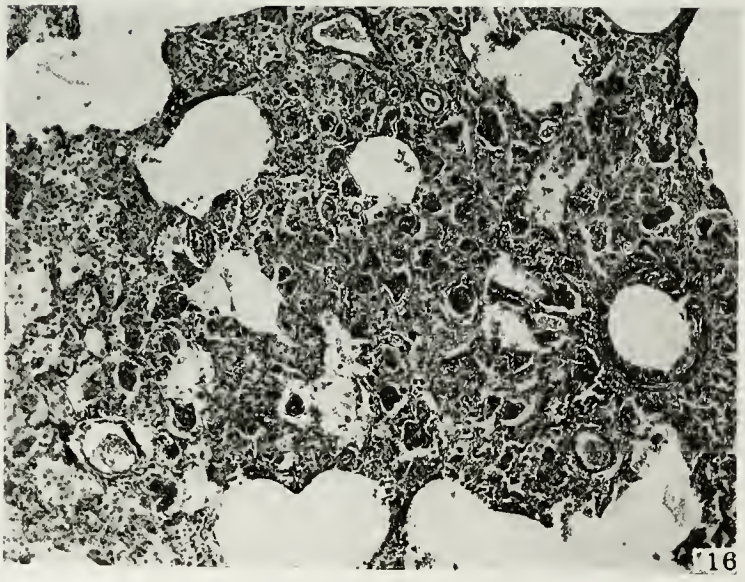

FIG. 9. SECTION OF LUNG SHOWING ALVEOLI FILLED WITH HYALINIZED FIBRIN IN A DOG DYING 10 DAYS AFTER EXPOSURE.

SUMMARY

The tremendous edema and congestion of the first stage subside with gradual recovery of the animal. An infectious process may be superimposed upon the impaired tissue in the form of a lobular pneumonia. The emphysema and atelectasis, associated with the bronchiolar changes, persist to some extent.

GROUP III. *Animals Which Survive Longer than 2 Weeks and Are Sacrificed up to 5 Months.*

No external changes are seen in this group. The abdominal viscera show nothing of note. The slight cardiac dilation observed in the first stage has disappeared, and there are no observable permanent lesions of the heart. The upper respiratory tract is normal in every respect, and an inflammatory process has never been observed in the larynx, trachea, or bronchi.

The lungs collapse when the thorax is opened. They are air-containing, elastic, and soft, and have a delicate, salmon-pink color. Not infrequently, small, red, puckered depressions are seen on the surface of the lung. Occasionally, firm, gray nodules a few millimeters in diameter are encountered in the lung tissue (see Phosgene paper).

Histologically, the greater part of the lung tissue appears normal. Here and there is seen a small group of alveoli over-distended with air (Fig. 10). Other groups are collapsed, with thickened interacinar walls infiltrated by small, mononuclear, wandering cells. The minute, gray nodules are found to be little islands of organized, fibrous tissue; sometimes a few smooth muscle fibers and blood vessels identify the spot as bronchiole, its lumen entirely filled with granulations, and no trace of epithelium remaining (Fig. 11); other nodules have no definite boundaries and appear to be groups of organized alveoli. The walls of the more normal bronchioles may show infiltration by mononuclear cells, and the lumina of the small bronchi frequently contain an excess of thick mucus in which there are a few cells.

SUMMARY

The lungs of animals which have recovered from poisoning by superpalite may exhibit a mild persistence of the atelectatic and emphysematous changes. The inflammatory process has largely resolved, but miliary foci of organized bronchiolitis and pneumonia remain.

DISCUSSION

Although the number of animals is too small to draw sweeping conclusions, the findings are in may respects confirmed by those of phosgene, a similar compound. In a large series of animals exposed to phosgene, many developed an intense, acute, necrotizing pneumonic process, but others showed only a mild, persistent, inflammatory reaction of the bronchioles and immediately surrounding alveoli. Both of these poisonous gases have relatively slight effect upon the upper respiratory tract, and in this way, differ from another group (chlorine, bromcyanogen, mustard gas), where intense inflammatory lesions of this area are the rule. It is natural to conclude that the intense inflammatory reaction in the trachea impairs the protective mechanism of the upper respiratory tract and is causally associated with the infectious pneumonia, which often kills within the first ten days after exposure to the latter group of gases. In the former group (superpalite, phosgene), where the trachea and bronchi are uninjured, an overwhelming pneumonia develops less frequently, but small, localized areas of infection may occur and result in chronic changes in the lung.

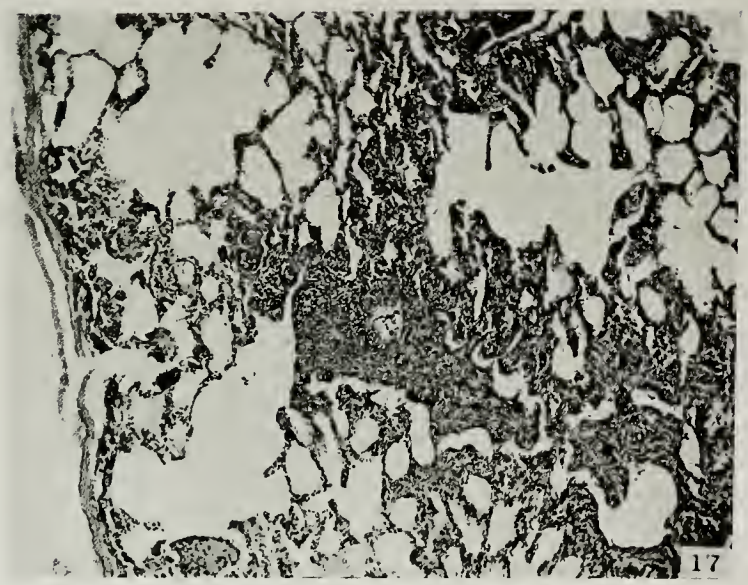

FIG. 10. SECTION OF LUNG SHOWING ORGANIZATION IN A BRONCHIOLE.

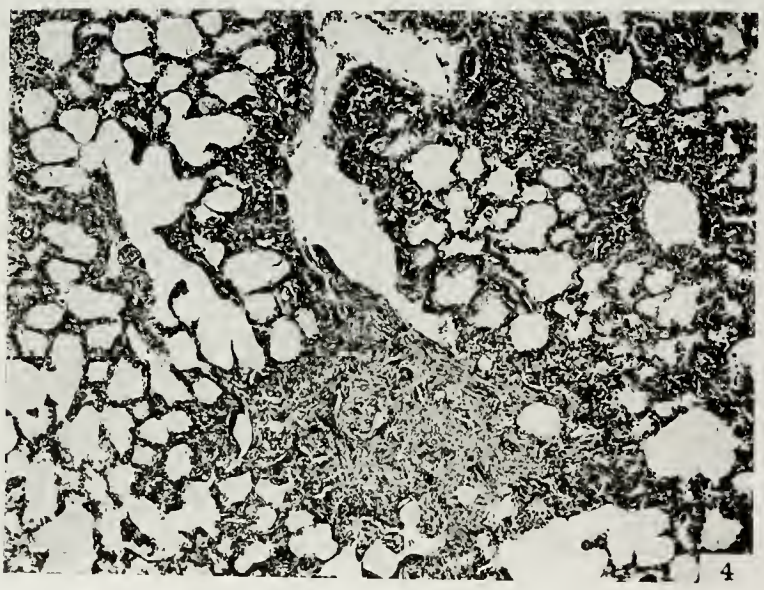

FIG. 11. SECTION OF LUNG SHOWING SCARRED AREA IN NEIGHBORHOOD OF A BRONCHUS.

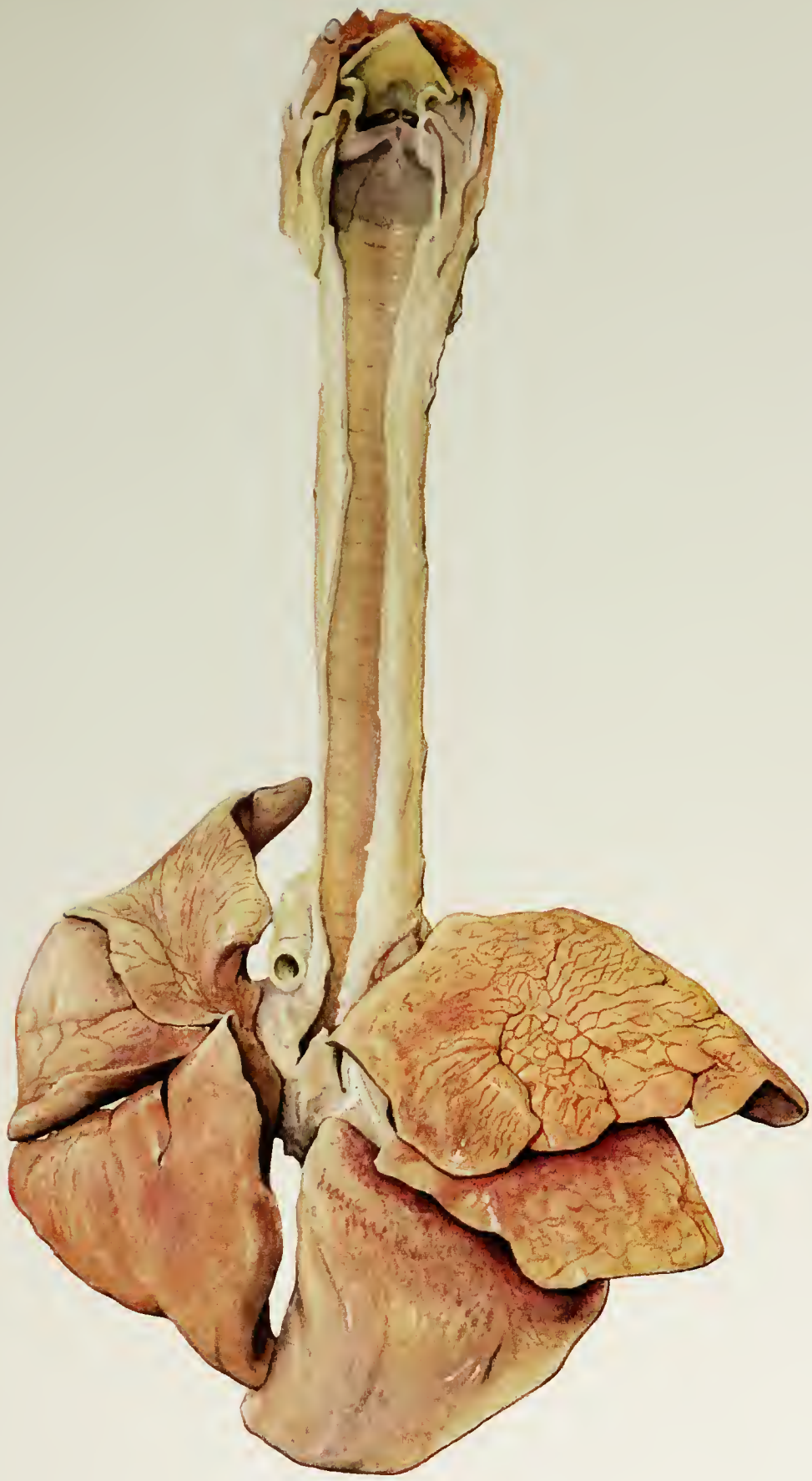

PLATE XIX

FIG. 8: LUNGS OF DOG SURVIVING 5 DAYS AFTER EXPOSURE TO SUPERPALITE, SHOWING DIMINUTION IN EXTENT OF EDEMA AND CONGESTION AND NEARLY COMPLETE DISAPPEARANCE OF ATELECTASIS AND EMPHYSEMA.

THE PATHOLOGY OF MUSTARD POISONING

BY

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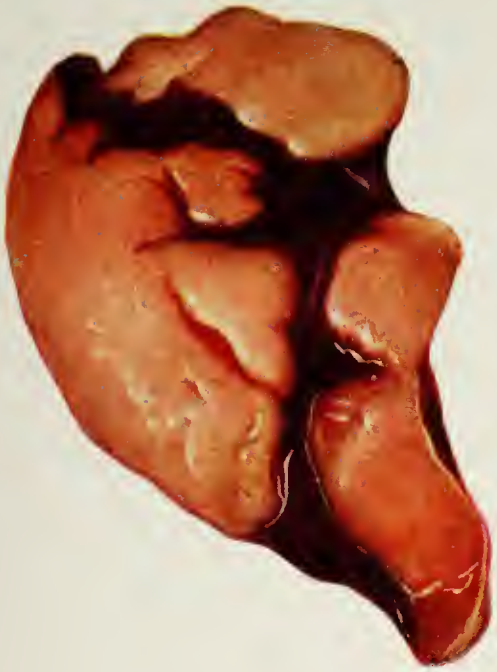
PLATE XX

FIG. 1: WATER COLOR DRAWING SHOWING LUNGS AND TRACHEA OF DOG DYING 37 HOURS AFTER EXPOSURE. THE LEFT UPPER LOBE IS COMPLETELY ATELECTATIC, THE RIGHT UPPER EMPHYSEMATOUS; THE LOWER LOBES ARE SOMEWHAT CONGESTED; THE MEMBRANE IN THE TRACHEA IS PEELING OFF IN PLACES.

PLATE XXI

FIG. 2: WATER COLOR DRAWING SHOWING LUNGS AND TRACHEA OF DOG DYING 2 DAYS AFTER EXPOSURE. THE LEFT UPPER AND RIGHT MIDDLE LOBES ARE HEAVY AND FIRM, SHOWING CONGESTION AND SOME ATELECTASIS; THE LEFT LOWER LOBE IS PUFFY AND EMPHYSEMATOUS; THE OTHER LOBES SHOW BOTH CONDITIONS AND HAVE SOME EDEMA. THE TRACHEA IS LINED BY SMOOTH MEMBRANE.



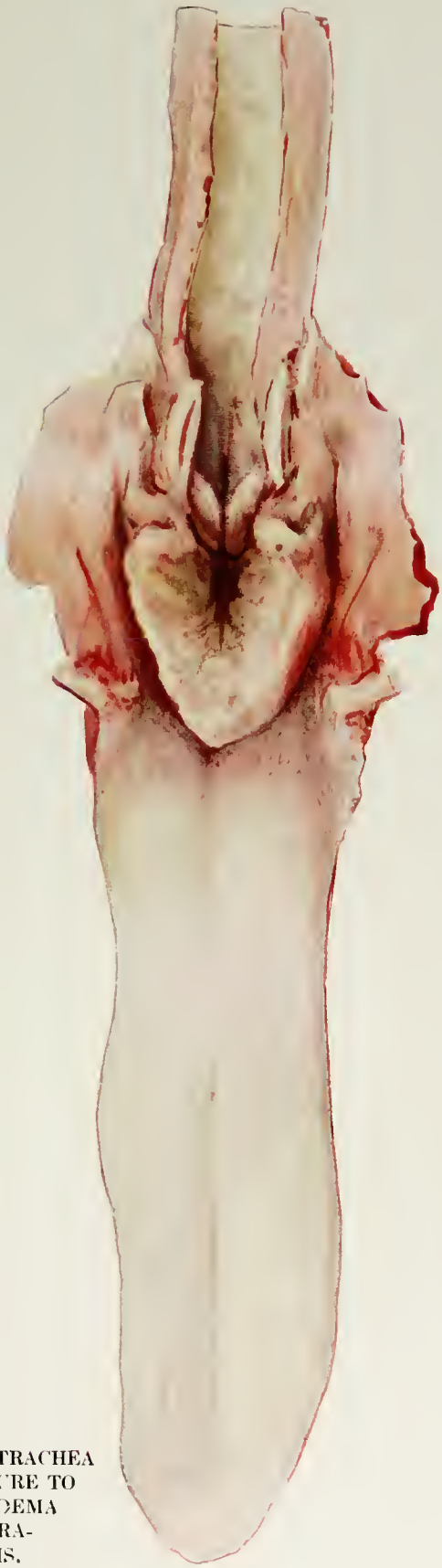


PLATE XXII

FIG. 3: LARGE AREAS OF ATELECTASIS IN AN EMPHYSEMATOUS LOBE OF A DOG'S LUNG. THE ANIMAL DIED ACUTELY AFTER EXPOSURE TO MUSTARD GAS.

FIG. 4: TONGUE, LARNYX, AND TRACHEA OF DOG 2 DAYS AFTER EXPOSURE TO MUSTARD GAS, SHOWING EDEMA LARYNX, MEMBRANOUS TRACHEITIS AND LARYNGITIS.

THE PATHOLOGY OF MUSTARD POISONING

Mustard gas differs from most of the other suffocating gases as its effects are not confined to the respiratory tract. While the most serious results are produced by the inhalation of the gas, there are also important subsidiary lesions caused by its action on the eyes and the skin. In the experiments here reported, most of the animals were exposed to the gas in an air chamber primarily to determine toxicity. Under these conditions all of the effects of the gas may be produced.

In the following report, the lesions of the respiratory tract will be presented in some detail as they are unquestionably of the greatest importance. The skin and ocular lesions will be only briefly discussed.

In a previous, unpublished report by G. M. Mackenzie, the pathological anatomy was studied in forty-nine dogs after exposure to lethal concentrations of several gases coming under the general name of mustard gas. The present report confirms, in general, Mackenzie's findings, but is based on the independent study of eight hundred dogs, some of which succumbed to acute poisoning and some of which recovered and were sacrificed at intervals up to five weeks after exposure to the gas. Only the compound dichlorethylsulphide is here included in the term "mustard gas," but many different samples of this compound have been used in both the pure and crude state.

SYMPTOMATOLOGY

The animals were gassed under the direction of Drs. E. K. Marshall and A. S. Loevenhart. The following is a brief summary of their observations on the behavior of the animals during and after gassing:

During exposure to mustard gas, the animals show no especial discomfort or excitement, but are usually drowsy. There are signs of mild irritation of the mucous surfaces; the eyes lachrymate; after a longer interval the nasal and salivary secretions are increased; and there is frequently irritation of the skin, particularly about the genitals. There is no sign of bronchial or laryngeal spasm, no choking or coughing, no tremors or convulsions.

For the first few hours after exposure, there is no marked change in condition. The animals are somewhat depressed, have no appetite, usually vomit, and have diarrhea, which may be blood-tinged. The eyes are red and apparently cause some discomfort.

About eight to twelve hours after exposure, a marked change in the pulse is noticed. In typical cases there is a slow rate (60-80) and irregular rhythm, though occasionally the pulse is fast and irregular. This effect passes off, and after the second day, the pulse either returns to normal or becomes rapid and irregular until death.

Respiratory changes begin after about the same interval required to affect the pulse (8 hours). The respiration becomes irregular and labored, usually not rapid; expiration

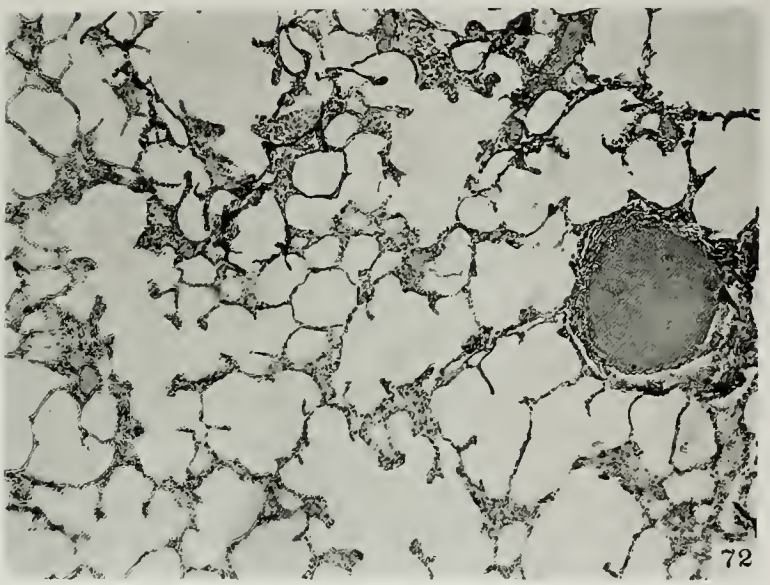


FIG. 5. EMPHYSEMA AND CONGESTION IN LOWER LOBE OF DOG DYING 24 HOURS AFTER EXPOSURE.

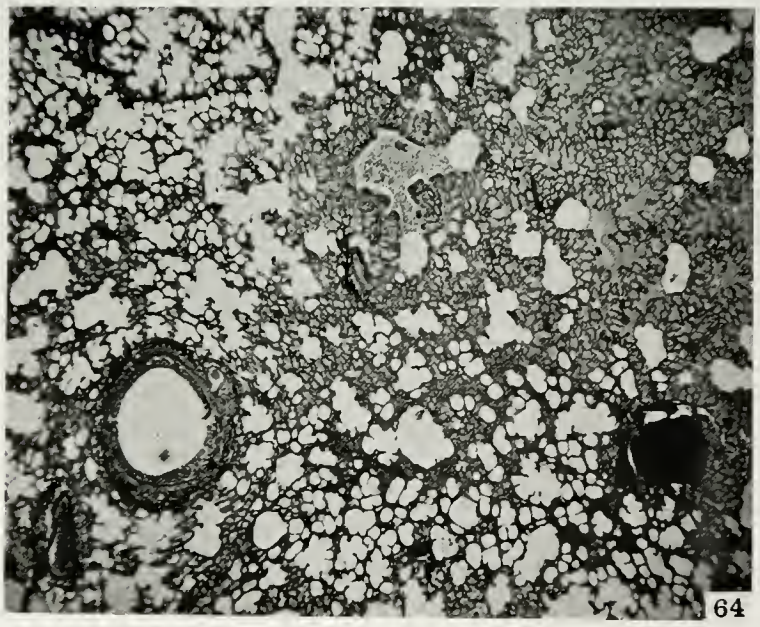


FIG. 6. SLIGHT EDEMA AND EMPHYSEMA IN UPPER LOBE OF DOG DYING 52 HOURS AFTER EXPOSURE.

seems difficult and is often stridulous; coughing is frequent. Salivation is profuse, but not frothy; nasal discharge is usual.

The early congestion of the conjunctivæ usually develops into a purulent discharge, and the cornea may become milky and opaque.

The animals rarely die in less than eighteen hours after exposure, but thereafter may die at any interval up to two weeks without ever having regained a normal condition. Most of the deaths occur during the second and third days. If the acute effects are recovered from, the animals may live indefinitely, with or without the chronic lesions to be described below.

PATHOLOGICAL ANATOMY

For convenience of discussion the material may be divided into three groups:—

GROUP I. *Animals that die without extensive pneumonia in 18 to 73 hours after exposure.*

GROUP II. *Animals that die with extensive pneumonia 2 to 10 days after exposure.*

GROUP III. *Animals that show symptoms after exposure but recover and are killed 1 to 5 weeks later.*

GROUP I. *Animals that Die Without Extensive Pneumonia in 18 to 73 Hours After Exposure.*

Externally, there are no marked lesions. The conjunctivæ are red and congested, but the corneæ are smooth and transparent. The mucous membranes just inside the lips may show congestion but not ulceration. The skin of the body is not usually affected, but sometimes the scrotum or vulva is red and swollen. "Wherever the hair is scant, the skin shows a bright red discoloration, without, however, the formation of vesicles. . . . Dogs show this dermatitis about the lips, nose, vulva, nipples, and between the toes" (Mackenzie). These lesions have been observed in occasional animals in our series but are by no means constant. They may be dependent on the type of compound or the concentration of the gas.

On opening the *thorax,* the lungs collapse only slightly, but the different lobes vary greatly in this respect. The pleural cavities contain no free fluid. The pleural surfaces are smooth and glistening.

The typical appearance of the different lobes is described below, but it must be understood that the locations of the different conditions may be reversed (Figs. 1 and 2). The lower lobes are the most voluminous and are of a curious, light, dusky, reddish purple color; they are very light in weight and are air-containing throughout. When they are handled, the fingers sink in and leave indentations in the tissues. There seems to be a complete loss in elasticity of the lungs, and the air sacs remain distended until some pressure is exerted from the outside. When these lobes are sectioned, the knife cuts through the distended air-containing tissue very easily. The cut surface is dry. The only striking feature is the great engorgement of the blood vessels with thick, dark blood, which, in the larger vessels, has formed semi-solid post-mortem clots.

The upper lobes present a quite different picture; their color is a brighter red but it is not uniform; there are many light pink, air-containing, and emphysematous areas alternating with darker, firm areas, which may be slightly sunken on the surface (Fig. 3). These lobes are heavier than the more voluminous lobes, are more elastic, and are not easily in-

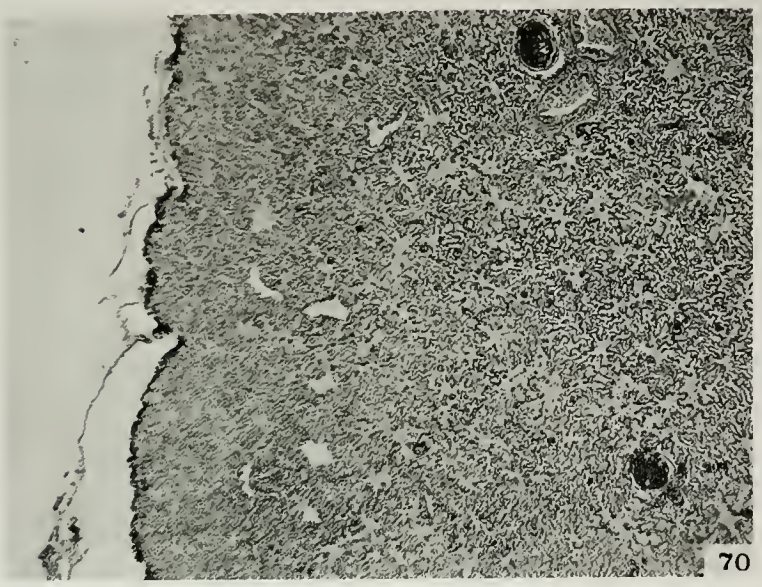


FIG. 7. ATELECTATIC LOBE OF DOG DYING 24 HOURS AFTER EXPOSURE, SHOWING CONGESTION OF CAPILLARIES WITH SLIGHT EDEMA.

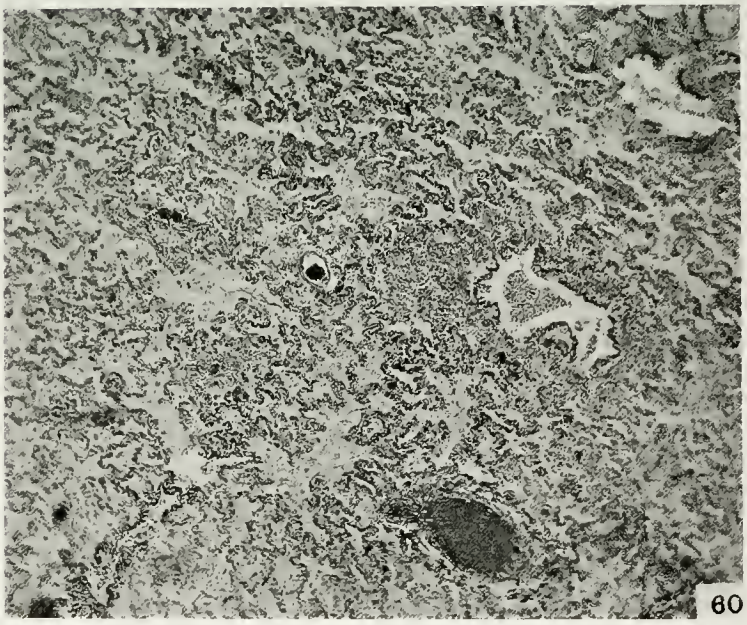


FIG. 8. SAME LOBE AS THAT OF FIG. 7.

dented by the fingers. On section, the cut surface remains flat but is rather wet. The engorgement of the blood vessels is not as striking, although there is marked congestion. There is a slight amount of edematous fluid, which can be scraped from the surface. The dark red areas which are seen on the surface extend through the lung tissue; in consistence they are almost like muscle, rubbery and firm, but with no visible pneumonic exudate in the alveoli. These are areas of localized atelectasis.

There is another condition found most commonly in the left, middle, and caudate lobes. The entire lobe is collapsed, dark red or almost black in color, uniform in consistency, firm and rubbery. On section, the tissue cuts and feels like blood agar. The color is so dark as to obscure all architecture; there does not seem to be any air at all in the lobe, but it floats when placed in water; the blood vessels are congested but not over distended as in the lower lobes.

When the large bronchi and trachea are opened, a yellowish gray, false membrane is found forming a complete cast of the bronchial tree (Figs. 1 and 2). This peels off from the underlying surfaces easily, and can often be pulled out intact for a length of several centimeters. In one or two cases, the dog coughed up a large piece of this membrane during life. The surface beneath the membrane is smooth, red, and sometimes hemorrhagic. The condition extends up as high as the vocal chords in all cases, and sometimes there is marked edema and inflammation of the epiglottis (Fig. 4). It has been claimed that this membrane completely plugs the bronchi which lead to the atelectatic lobes, and is the cause of the atelectasis. In the same way, it might account for the puffy condition of the lower lobes, as the air in the alveoli cannot escape when the thorax is opened. While this seems the most logical explanation, it must be confessed that we have not been able to prove it by dissection. Sometimes the bronchus leading to the atelectatic lobe is conspicuously free from exudate, and the tracheal membrane covers the entrance to this bronchus. This may indicate that the membrane was formed after the current of air passing in and out of the bronchus had ceased. In other cases there is a thick mass of exudate and membrane in the lumen of the bronchus, but this has never been found fitting in tightly enough to distend the bronchus to a round shape; the bronchus is always collapsed. The membrane at the entrance to the other non-atelectatic lobes is equally thick and tough.

Microscopically, the parenchyma of the different lobes corresponds to the gross picture. The lower lobes show practically normal, air-containing alveoli, which are of fairly uniform size, showing very little local emphysema or atelectasis (Fig. 5). The only strikingly abnormal condition is the enormous engorgement of the blood vessels, both small and large, which is present everywhere. The terminal bronchioles are for the most part normal but may show dilatation and epithelial necrosis. The larger bronchi will be described below. The upper lobes, which have alternating areas of emphysema and atelectasis in the gross, show a corresponding microscopic picture. Here, also, there is marked engorgement of the blood vessels. Over rather small areas there is edema of the lung tissue and the air sacs are filled with a pink-staining, homogeneous fluid (Fig. 6). In the atelectatic lobes there is surprisingly little pathological change to be seen under the microscope. The alveolar walls with their capillaries engorged are somewhat thickened and tortuous and lie close to each other. The air space is almost obliterated (Figs. 7 and 8). The bronchi often contain rather thick mucus and fibrinous exudate, which may be etiologically associated with the atelectasis.

The larger bronchi and trachea are most interesting. Beginning with the trachea, the epithelium has usually been destroyed all the way around its circumference, but oc-

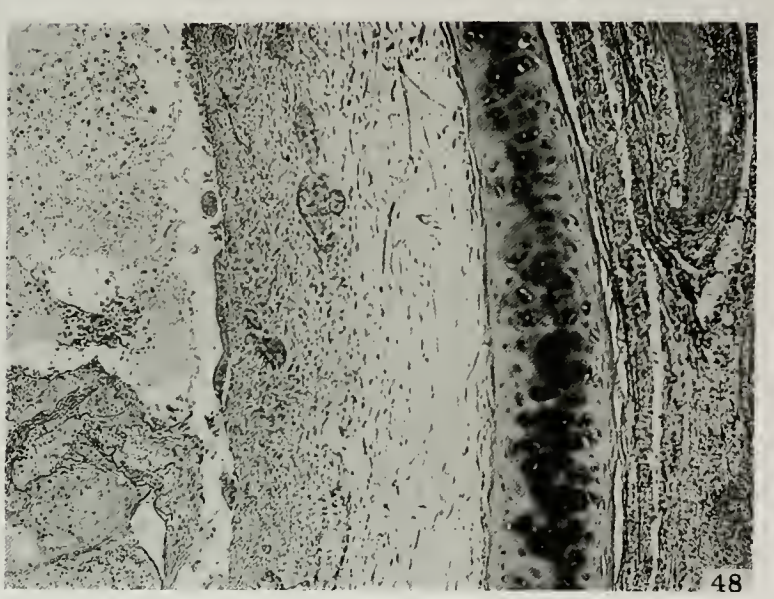


FIG. 9. INFLAMMATION OF TRACHEA; EPITHELIUM STILL SHOWS IN SPOTS. DOG DIED 24 HOURS AFTER EXPOSURE.

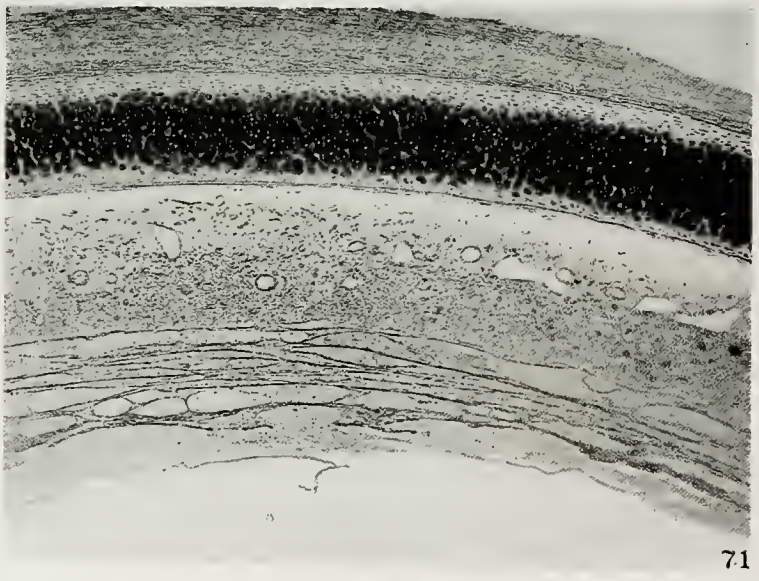


FIG. 10. SAME TRACHEA AS THAT OF FIG. 9, SHOWING EPITHELIUM ENTIRELY DESTROYED.

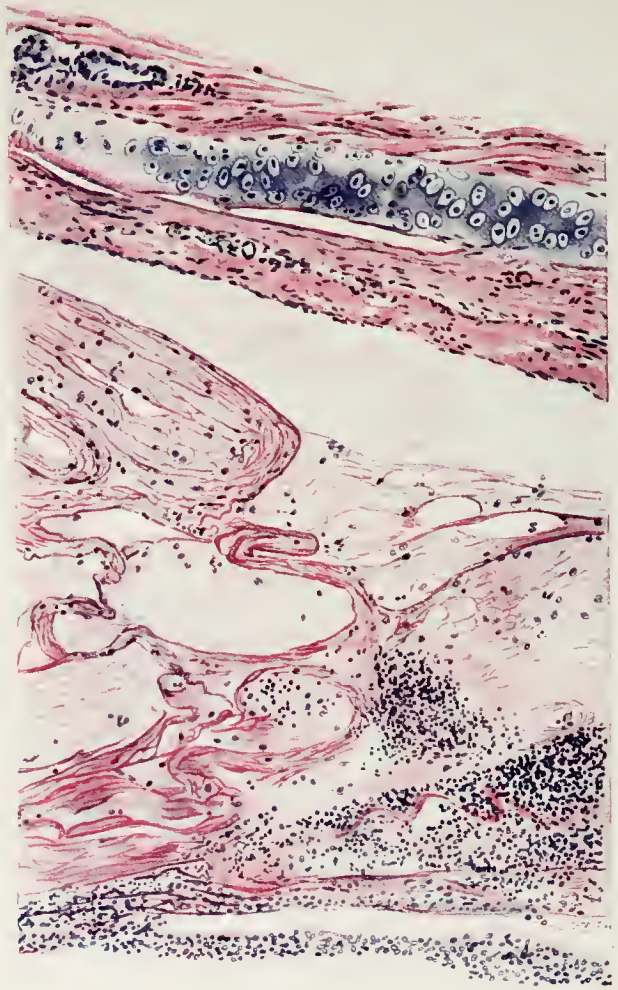


FIG. 11: WATER COLOR DRAWING OF TRACHEA OF DOG DYING 25 HOURS AFTER EXPOSURE: THE EPITHELIUM IS ENTIRELY DESTROYED. THE SUBMUCOSA IS EDEMATOUS WITH LARGE FIBRIN SPACES AND MANY LEUCOCYTES.

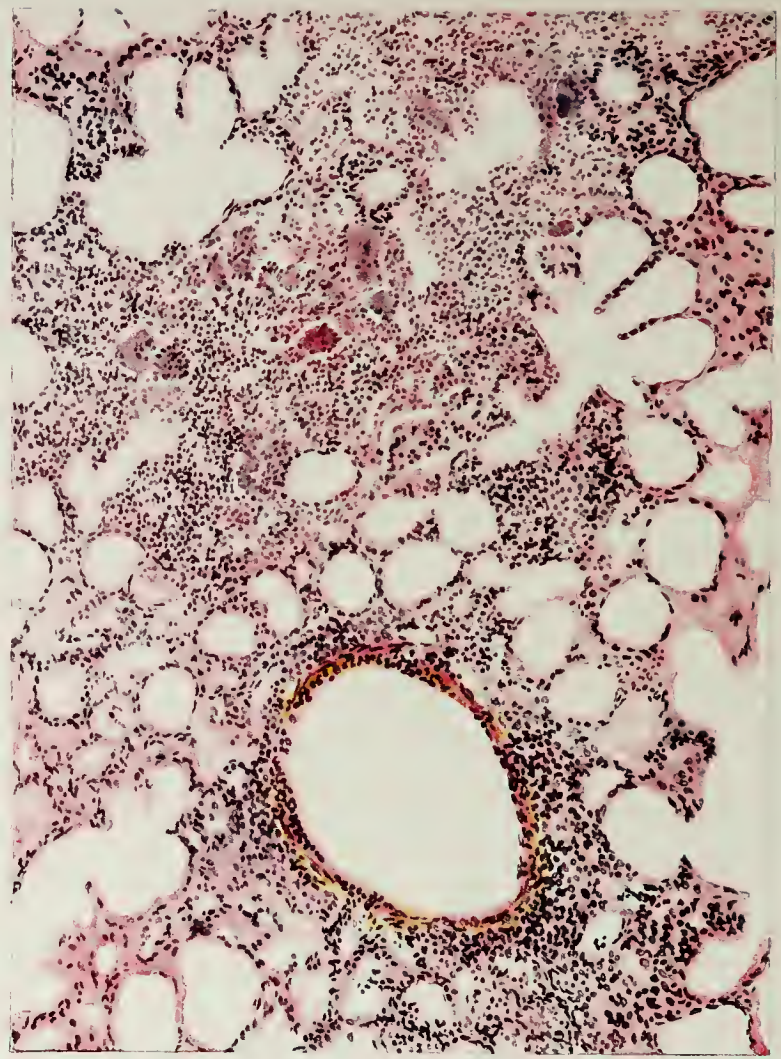


PLATE XXIII

FIG. 16: DILATATION OF SMALL BRONCHUS WITH EPITHELIAL NECROSIS; SMALL MASSES OF BACTERIA (TO LEFT) WITH LEUCOCYTIC INFILTRATION. DEATH 72 HOURS AFTER EXPOSURE.

casionally it is still intact over the posterior or upper side of the trachea where the cartilage is lacking. The membrane is always thicker over the anterior or dependent side of the trachea and possibly gravity plays a part in producing the difference. This membrane (Figs. 9 and 10) consists of necrotic epithelium and cell débris, fibrin, leucocytes, mucus, and, occasionally, red cells. It is rather light in texture and pink-staining but sometimes has dense purple-staining masses typical of necrosis mixed with mucus and bacteria. As a rule, the underlying submucosa shows edematous tissue spaces, which may contain a fibrin network; this never attains the astounding proportions seen in some other gases (Fig. 11). The walls of the trachea are frequently infiltrated by polymorphonuclear leucocytes, both within and without the cartilaginous rings. This condition extends into the bronchi without change in its essential characteristics. The lumina of the bronchi contain large masses of necrotic material in which leucocytes are more numerous than in the trachea. The edema is almost absent. There is only occasionally a clump of fibrin seen in the bronchial walls or lymph spaces. The polymorphonuclear infiltration of the walls is still a conspicuous feature (Fig. 12).

Although there is no extensive lobular pneumonia in the gross, dogs dying as early as 24 hours after exposure often show areas of leucocytic infiltration associated with deposits of serum and fibrin in the alveoli. Such exudations have a tendency to zonal distribution about the bronchi. In such areas the walls of the terminal bronchiole as well as the surrounding alveolar walls stain diffusely pink, indicating necrosis (Figs. 13 and 14).

There are often small areas of hemorrhage into the lung tissue, with the alveoli full of red cells. These areas are often, but not always, in the atelectatic lobes (Fig. 15).

By bacterial stains it can be demonstrated that Gram-positive cocci are already present in clumps in the necrotic epithelium of the small bronchi far down in the lung parenchyma, or are even seen outside the walls of the bronchi in the immediately adjoining tissue without marked inflammatory reaction around them (Figs. 16 and 17). There are large numbers of bacteria, chiefly cocci, present in the trachea and larger bronchi. Bacteriological cultures were not begun until toward the end of the series and have not been sufficient to warrant definite conclusions. It may be said, however, that the prevailing organism is nearly always a Gram-positive coccus, frequently a staphylococcus.

In the *heart* no lesions have been found either in the muscle or in the conducting system. Some hearts have been saved for a more careful study of the bundle of His. The right side of the heart is usually found slightly distended and is filled with a very dark, soft, post-mortem clot. The left side is usually contracted and contains little clot.

The *abdominal organs* aside from the marked congestion, show no characteristic lesions. The liver is large, dark red, and firm, and on section, much dark blood runs forth. The spleen is light red in color, and the Malpighian bodies are scarcely visible; the splenic pulp is rather soft. The kidneys are dark red and firm; the capsule strips readily, and on section, the architecture is beautifully distinct. The congestion extends throughout but is more marked in the cortex. The adrenals, besides sharing in the general abdominal congestion, frequently show minute punctate hemorrhages in the cortex or at the line where the cortex joins the medulla. The medulla is sometimes soft and dark red as though hemorrhages into it had taken place. The intestinal tract may also show congestion of the mucosa, particularly in the duodenum and colon. We have not found definite hemorrhages into the intestinal lumen attributable to the effects of gassing in a chamber.*

* In about 75% of the animals autopsied, the *Anchylostoma caninum* have been found attached to the mucosa of the small intestines in large numbers; these worms are frequently surrounded by

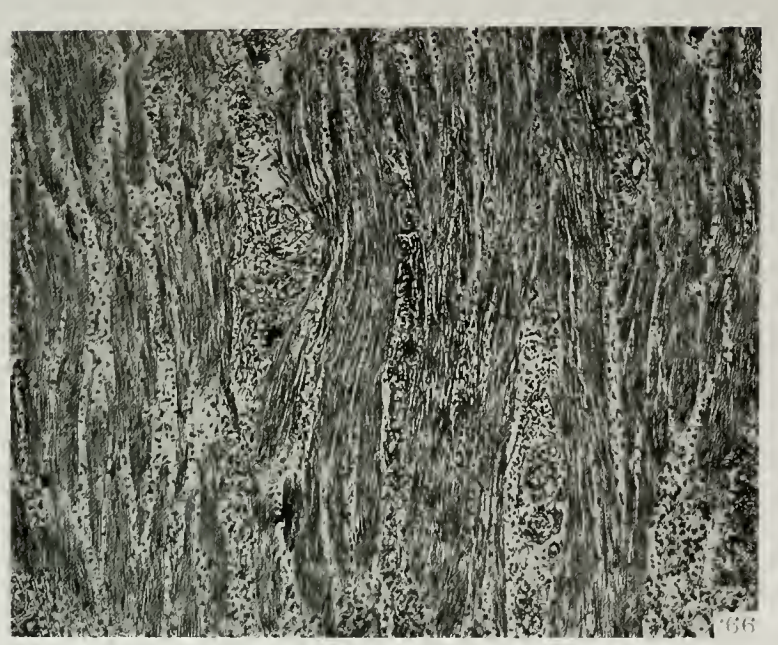


FIG. 12. TANGENTIAL SECTION OF LARGE BRONCHUS SHOWING LEUCOCYTIC INFILTRATION; DEATH 24 HOURS AFTER EXPOSURE.

FIG. 13. DILATATION OF TERMINAL BRONCHIOLES AND ALVEOLI, WITH NECROSIS OF ALVEOLAR WALLS; EDEMA, RED CELLS, FIBRIN AND LEUCOCYTES FORM THE EXUDATE.

SUMMARY

Dogs that die in the first acute stages after exposure to the gas show marked congestion of the lungs with little edema. Atelectasis is present in some lobes or parts of lobes. There is great destruction of the epithelium of the upper respiratory passages, with false membrane formation and beginning invasion by bacteria. This usually extends to the bronchioles. Necrosis of their walls, as well as those of the surrounding alveoli, occurs with hemorrhage and early inflammatory exudate in the vicinity.

GROUP II. *Animals That Die with Extensive Pneumonia 2 to 10 Days After Exposure.*

In the first group, an attempt was made to separate the animals which show acute pulmonary changes but in which, although bacteria are present in small numbers, there is no extensive pneumonic exudate.

In contrast to these are dogs which live a little longer, especially a few days longer, and show broncho-pneumonia variable in extent, involving parts of one or many lobes (Fig. 18 and 19).

The *large bronchi* and *trachea* now have a thick purulent exudate in addition to the membrane; or the membrane may have sloughed off, leaving a slightly roughened surface devoid of epithelium, red, and covered with pus. In two dogs, the tracheal surface has presented a yellow, granulating appearance as though healing processes had begun.

The congestion of the *abdominal viscera* may have given place to cloudy swelling, and sometimes fatty change is well marked in the liver.

Chronic inflammatory lesions of the *eyes* are frequently observed in this group, but play no important part in causing death.

Microscopically, the pneumonic areas may show central necrotization and abscess formation; the leucocytic exudation is profuse and extensive. In the trachea, the submucous layer shows an infiltration with plasma cells and other chronic inflammatory cells (Figs. 20 and 21). Early regeneration of the tracheal epithelium is occasionally seen.

SUMMARY

Animals that die from two to ten days after exposure to the gas have an extensive necrotizing broncho-pneumonia.

GROUP III. *Animals That Show Symptoms of Intoxication After Exposure but Recover and Are Killed from 1 to 5 Weeks Later.*

Many animals were exposed to concentrations so low that at no time did they show characteristic symptoms. Autopsies on these animals show no lesions. Other animals recovered and apparently would have lived indefinitely; although they showed characteristic symptoms after exposure, namely, irritation of the eyes, loss of appetite for a week or more, irregularity of the pulse, and some respiratory distress. In about 75 per cent. of these animals, chronic lesions are found; of these, the great majority are lesions of the eyes with but few of the respiratory tract.

The most common lesion is an ulceration of one or both *corneæ*. There may be a dif-

a bloody, mucous exudate. The numerous other intestinal parasites have no visible effect on the mucosa.

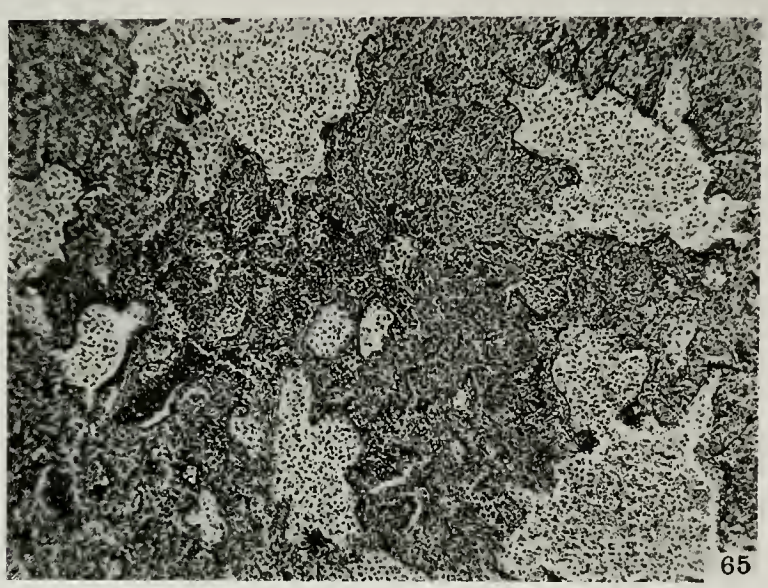


FIG. 14. EARLY PNEUMONIC EXUDATE OF POLYMORPHONUCLEAR LEUCOCYTES.

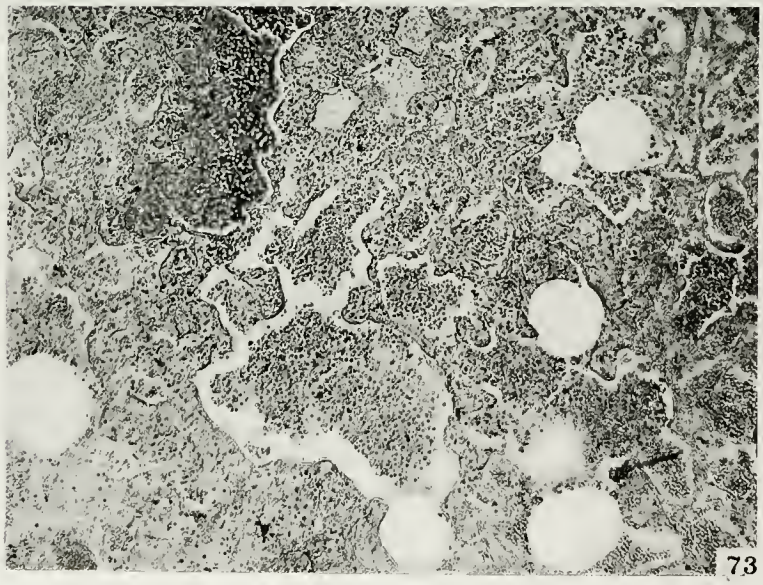


FIG. 15. HEMORRHAGE INTO LUNG, ALVEOLI FULL OF RED CELLS. EXUDATE CONTAINS NO LEUCOCYTES.

fuse keratitis producing a milky opaque cornea, which remains after the subsidence of the purulent conjunctivitis. More often there is ulceration of the cornea over the anterior chamber of the eye; a red, granulating area 4 or 5 mm. in diameter, or covering the whole cornea, appears. Hypopyon accompanies the ulceration. In two cases perforation of the chamber occurred, with extrusion of the lens. In others the granulating area undergoes healing with scar formation and adhesions between the lens and the cornea. Many of these lesions produce blindness and may be found in one or both eyes (Figs. 22 and 23).*

In three dogs localized ulcerating areas were found in the *trachea* and *larynx*. The ulcers were a few millimeters to one centimeter in diameter, crater-like, with granulating edges. Under the microscope, the ulcers presented a rough, granulating surface, with infiltration by polymorphonuclear cells and round cells extending through the muscular coats of the trachea. In one case there was erosion of the cartilage, with abscess formation deep in the tracheal wall.

In two dogs constrictions of the trachea have been found a few centimeters below the larynx, which apparently had been produced by contracting bands of scar tissue (Fig. 24). The sub-mucous coat at these points was thick and fibrous. The epithelium of the trachea was intact. The stenosis of the trachea was sufficient to cause noticeable respiratory distress when the animals were made to exercise, and barking had been reduced to a hoarse, wheezing noise.

Chronic changes in the *lungs* were infrequent, and were confined to minute areas of organization occurring in isolated bronchioles or in the alveolar tissue near the margins of the lungs (Fig. 25). In no case, was any large bronchus found organized or occluded; nor did areas of atelectasis or emphysema persist.

Chronic lesions of the *skin* have not been found. In the mouth, the mucous membrane just inside the lips has occasionally shown superficial ulceration.

In three dogs, which died respectively, 1 day, 7 days, and 18 days after exposure to the gas, an entirely different condition has been found. There was a massive fibrino-purulent pleurisy, more extensive on one side than on the other, accompanied by a copious, thin, purulent, pleural effusion. It does not seem possible to show an etiological connection between exposure to the gas and this condition, especially as one dog died within 24 hours, and the pleurisy probably antedated exposure to the gas. A similar condition has been found developing spontaneously in two dogs which died in the kennels before being used for experiment. Nevertheless, it is quite conceivable that such a pleurisy or empyema might follow the infectious pneumonia described under Group II.

SUMMARY

The chronic lesions in dogs which recover from acute poisoning are in order of frequency: ulceration of the cornea resulting in blindness, ulcerations or constrictions of the trachea, superficial ulcerations of the buccal mucous membranes, and minute areas of organization in the lungs.

DISCUSSION

The division of animals into groups as has been done in the preceding report is an arbitrary classification influenced by a similar division made for such gases as chlo-

* "The Ocular Lesions Produced by Dichlorethyl-Sulphide: (Mustard Gas)" by A. S. Warthin, C. V. Weller, and R. G. Herrman, Jour. Lab. and Clin. Med., 1918, 4, 785.

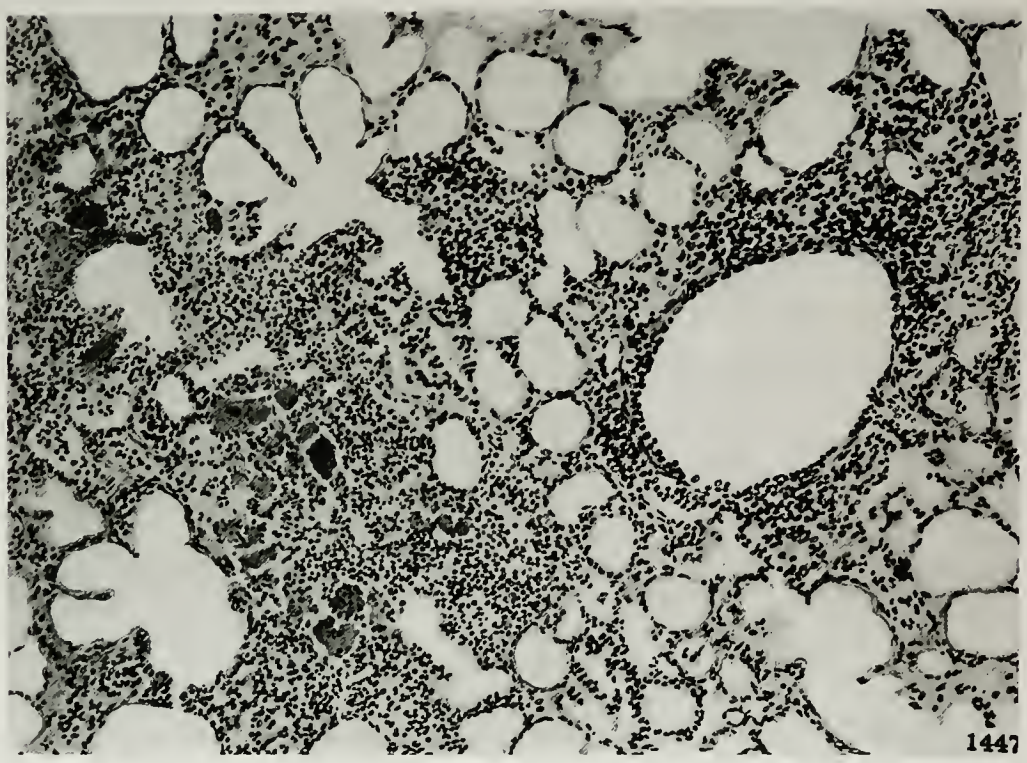


FIG. 16. DILATATION OF SMALL BRONCHUS WITH EPITHELIAL NECROSIS; SMALL MASSES OF BACTERIA (TO LEFT), WITH LEUCOCYTIC INFILTRATION; DEATH 72 HOURS AFTER EXPOSURE.

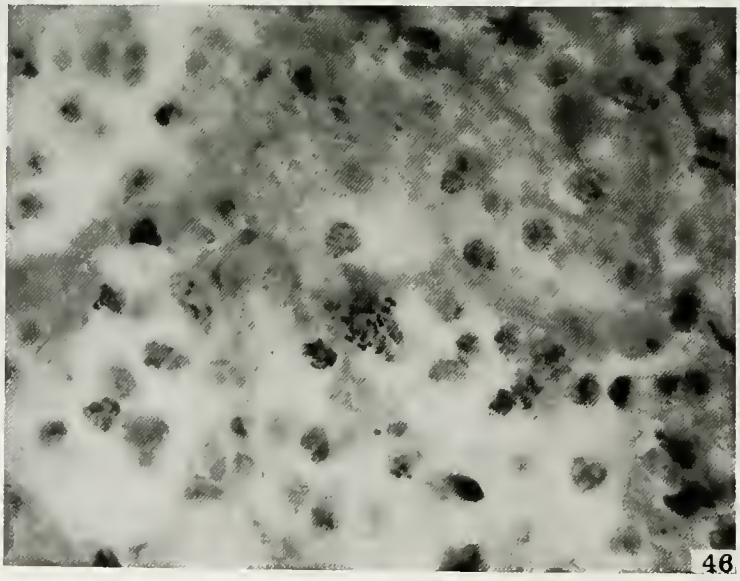


FIG. 17. SMALL GROUP OF COCCI IN LUNG 24 HOURS AFTER EXPOSURE.

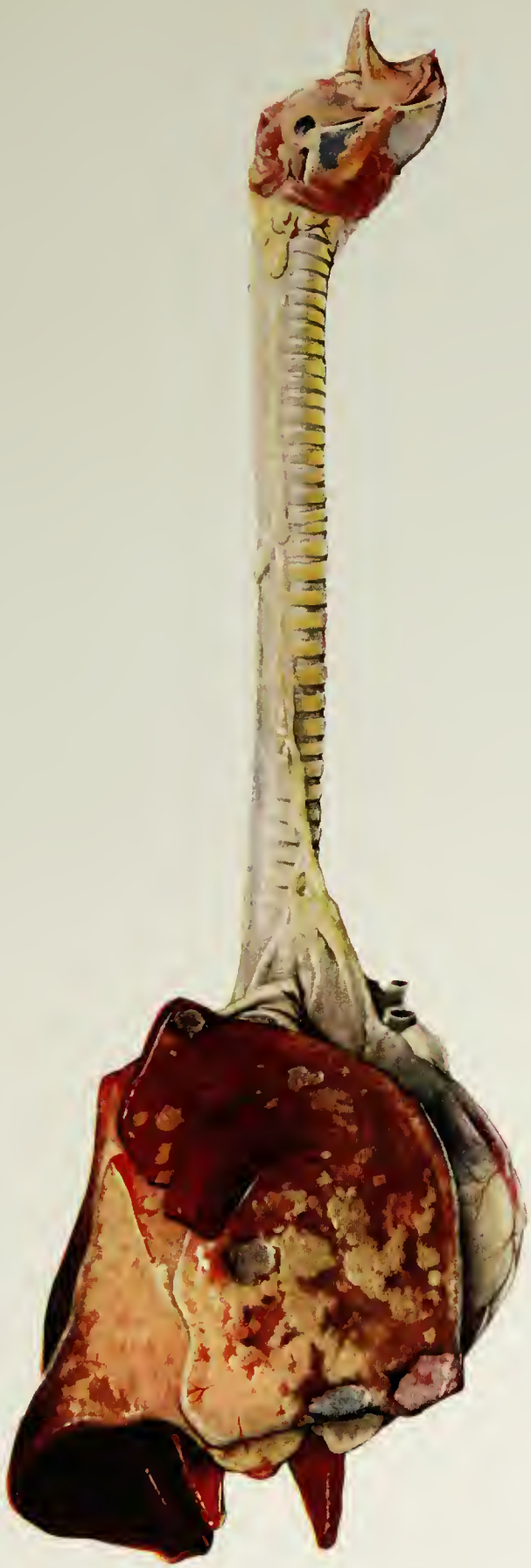
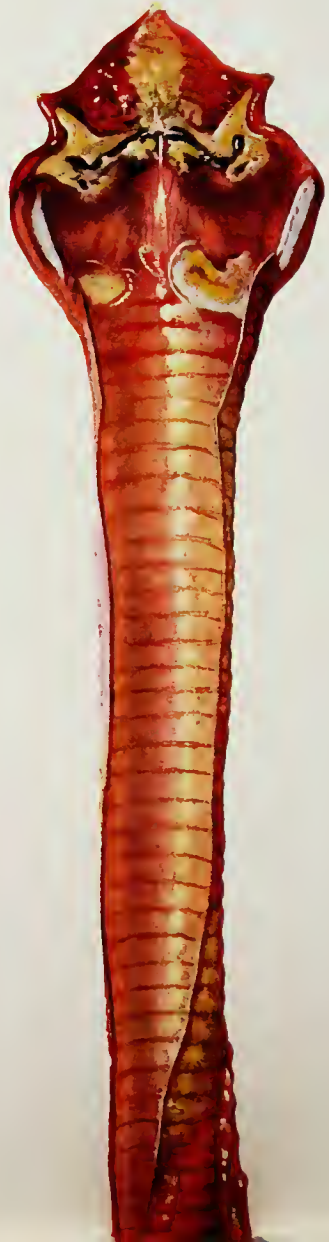


PLATE XXIV

FIG. 18: PNEUMONIA WITH EARLY ABSCESS FORMATION IN DOG DYING 5 DAYS AFTER EXPOSURE TO MUSTARD GAS.



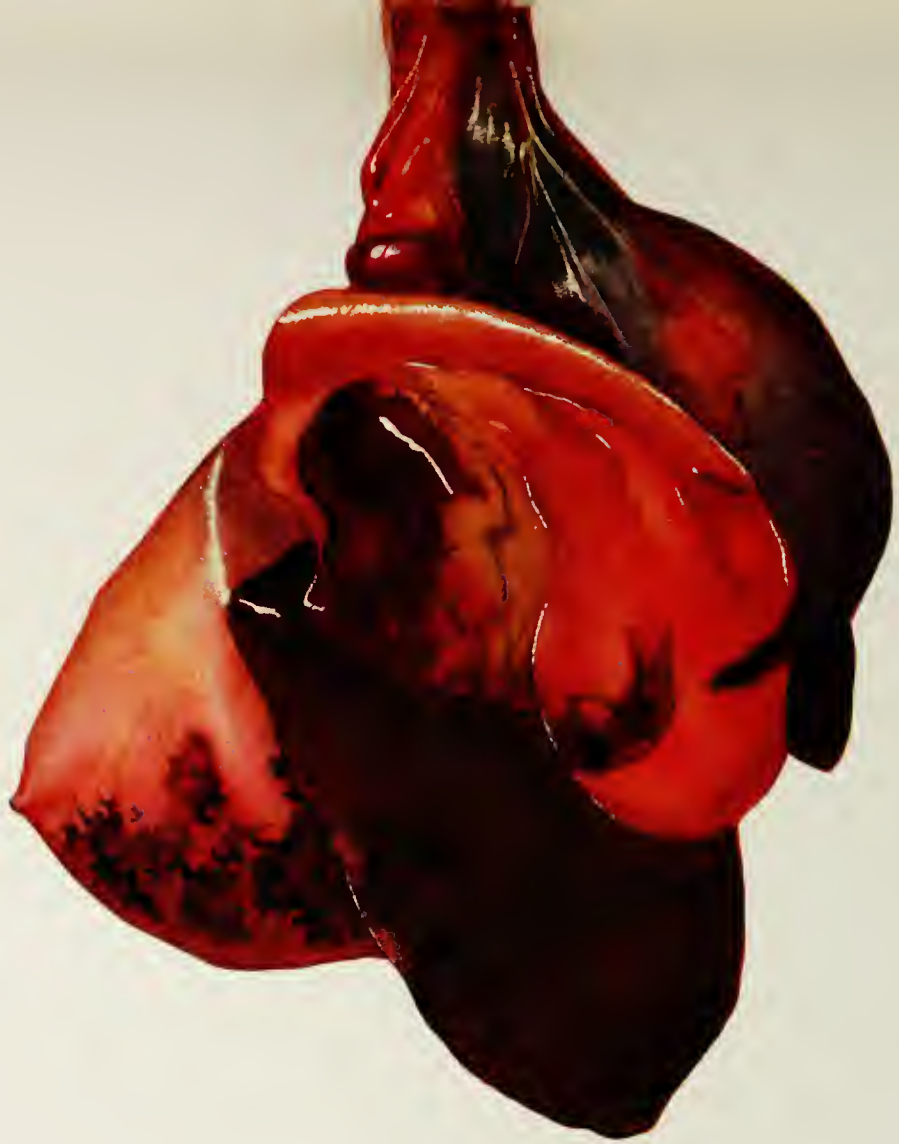


PLATE XXV

FIG. 19: NECROTIZING MEMBRANE OF EPIGLOTTIS AND LARYNX AND EXTENSIVE PNEUMONIA 5 DAYS AFTER A 30-MINUTE EXPOSURE TO MUSTARD GAS.

rine, phosgene, superpalite, and bromcyanogen, where this grouping seems to be a natural and sequential one. Difficulty is experienced in making this classification with mustard gas, inasmuch as there is no stage of edema which precedes the more active inflammatory exudation in the respiratory tract.

Mustard gas is an intense local irritant. Applied to such resisting surfaces as the skin, it causes necrosis with blistering and inflammatory exudation. On the moist and delicate mucous surfaces of the eyes and mouth, it is even more active. On the epithelium of the trachea and larger bronchi, it produces a most severe, destructive necrosis. But on the epithelium of the bronchioles and the alveolar walls, it would seem to have a relatively slight effect. The question arises whether this is due to some specific protective property of the epithelium for which there is no evidence, or whether the gas fails to reach these cells in the same concentration or in the same form in which it reaches the upper air passages. The only possible explanation for the occurrence of the pulmonary lesions after exposure to mustard gas lies in the fact that if the gas reaches the lung in sufficient concentration to produce extensive change, the animal will die in the acute stage. The gas may be broken down in the upper air passage or may be mechanically excluded by bronchiolar spasm from the alveoli. Certainly, the absence of chronic lesions can only be explained by the fact that when a sufficient amount of the gas is inhaled to produce extensive pulmonary lesions, the animal dies acutely.

The marked difference in the severity of effects produced in animals exposed to the same concentration of gas may be due in part to variation in individual suseeptibility, and in part to mechanical conditions which determine the amount of gas actually reaching the tissues; among these should be mentioned the behavior and activity of the animal while in the gas chamber.

Those animals which die in acute stages before the development of extensive pneumonia probably succumb as a result of the combined effects of destructive changes in the lungs and systemic effects from absorption of the gas. In cases in which there is some necrosis of the bronchioles and alveolar walls, the resulting infectious pneumonia is a natural sequel. Also, in those dogs in which there is extensive necrosis of the trachea and bronchi without involvement of the lung parchyma, it is natural that after a somewhat longer interval, autolysis of the massive exudate mixed with bacteria might give rise to areas of bronchopneumonia. It is conceivable that a degree of destruction and resultant exudation might occur, which would allow recovery of the animal with subsequent organization of the exudate in the bronchioles and pulmonary parenchyma. Finally, those animals which after several weeks show normal lung tissues can never have had extensive destructive inflammatory changes in the pulmonary parenchyma, and the effect of the gas must have been confined to localized areas of necrosis of the respiratory epithelium. While the regeneration of the tracheal epithelium has not been throughly investigated, we have seen abundant evidence that such processes may take place.

The pathology of skin lesions will not be taken up here, inasmuch as this subject has been very throughly discussed in a recent paper by Warthin and Weller.*

* Warthin, A. S., and Weller, C. V., "The Pathology of the Skin Lesions Produced by Mustard Gas (Dichlorethylsulphide)," Jour. Lab. and Clin. Med., 1918, *3*, 447.

FIG. 20. CHRONIC INFLAMMATORY CELLS INFILTRATING SUBMUCOSA OF TRACHEA; THE EPITHELIUM IS LACKING. DOG CHLOROFORMED 9 DAYS AFTER EXPOSURE.

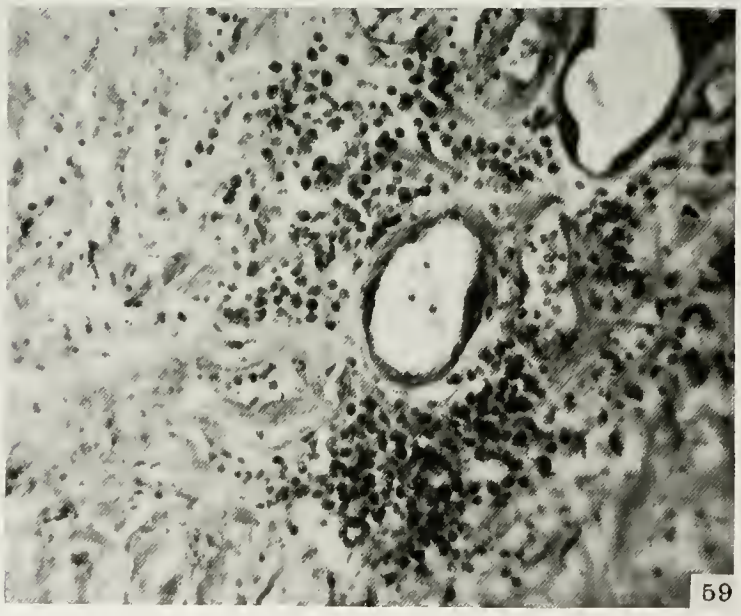


FIG. 21. SAME TRACHEA AS SHOWN IN FIG. 20.

FIG. 22: EYE OF DOG DYING 4 DAYS AND 21 HOURS AFTER EXPOSURE TO MUSTARD GAS (CONC. 0.323, DURATION 30 MIN.)

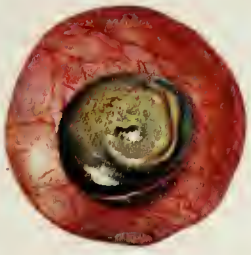


FIG. 23: EYE OF ANIMAL DYING 7 DAYS AFTER EXPOSURE TO MUSTARD GAS (CONC. 0.059, DURATION 30 MIN.)

FIG. 24: WATER COLOR DRAWING O_ TRACHEA SHOWING CONSTRIC- TION BELOW LARYNX; 1 MONTH AFTER EXPOSURE.

PLATE XXVI

THE PATHOLOGY OF CYANOGEN, CHLORIDE AND BROMIDE

BY

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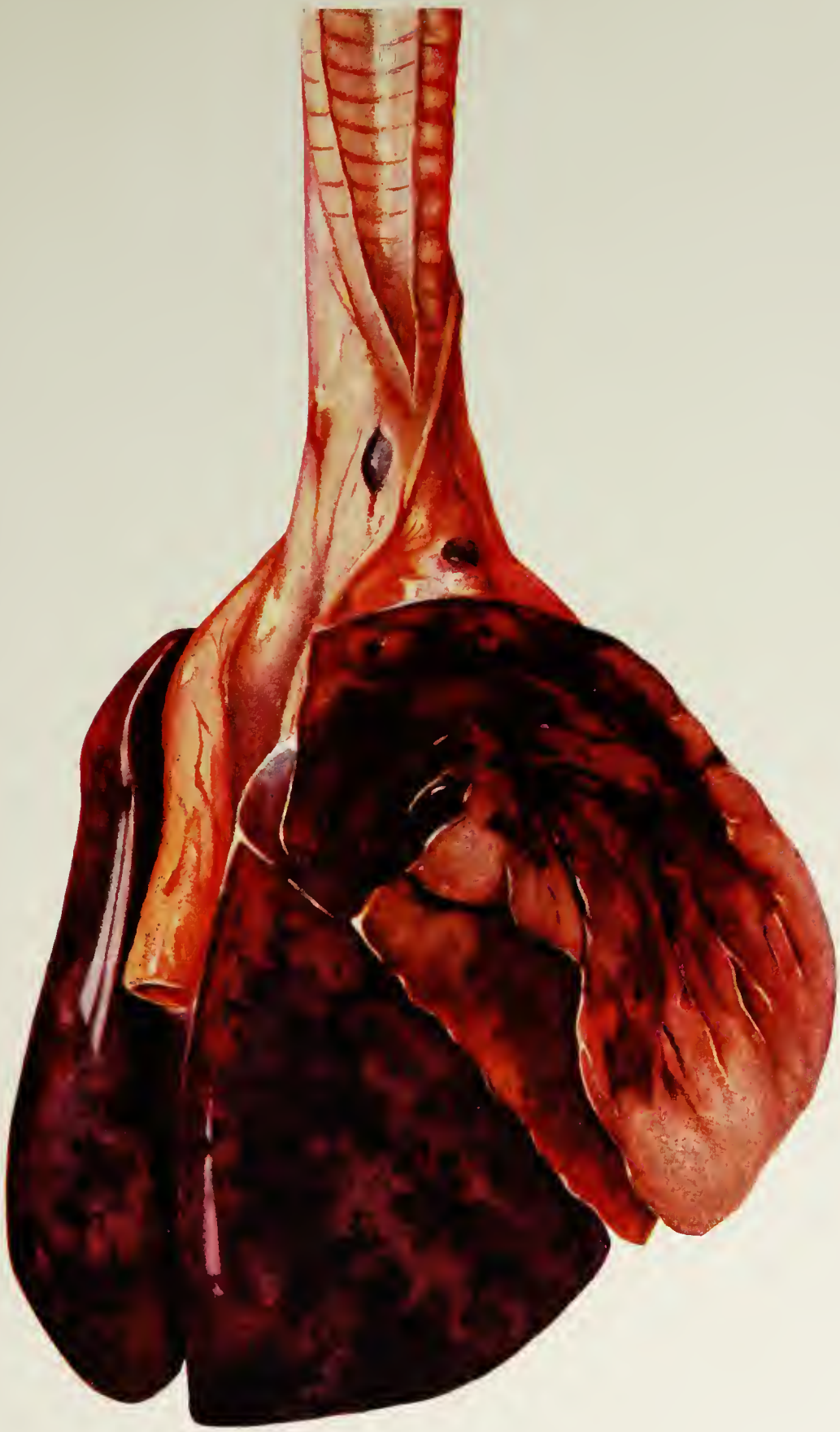

PLATE XXVII

FIG. 1: LUNG OF DOG, SURVIVING 5 HOURS, GASSED WITH A HIGH CONCENTRATION (1.73 MGM. PER LITRE) OF CYANOGEN CHLORIDE.

THE PATHOLOGY OF POISONING BY CYANOGEN AND ITS CHLORINE AND BROMINE DERIVATIVES

Fatalities from cyanogen and its salts are sufficiently common to have made the pathology familiar. "Poisoning from HCN results in a decreased consumption of oxygen and a decreased production of CO_2. This is due to the fact that when cyanide is present, the tissues lose their capacity to bind oxygen. The poisoning is an internal suffocation of the organs in the presence of increased oxygen" (J. Geppert, Ztschr. f. klin. Med. 1889, *15*, 347). In warm-blooded animals, including man, it not only inhibits the enzymic activities but also acts upon the central nervous system. In large doses, it involves all centers simultaneously, while in smaller quantities, after preliminary stimulation, it depresses first the respiratory and circulatory centers (R. Kobert, 1893, Lehrbuch der Intoxikationen, p. 513).

There are no distinctive lesions produced in poisoning by hydrocyanic acid. The blood has a bright red color, and on account of the delay in the post-mortem blood coagulation, a bright red lividity is manifest in the dependent parts. If potassium cyanide reaches the stomach undecomposed, it forms with the hemoglobin a striking red or blue cyanmethemoglobin compound. The mucous membrane is soapy, slippery, covered with blood-tinged mucus, swollen, and transparent at the crests of the folds. This is supposed to be characteristic and is brought about by the alkaline action of the potassium (E. Kaufman, 1909, Lehrb. d. spez. Path. Anatomie, p. 418). It is claimed by Kobert (p. 516) that increased pressure in the ventricles of the brain may occur in the more delayed action of the poisoning. The right heart is usually distended, the left empty. Post-mortem digestion sets in rapidly, especially in the liver. The lungs may be edematous, and the urine may contain blood and sugar.

There is no essential delayed action of HCN, and experimental results (E. K. Marshall) indicate that if an animal does not succumb during exposure to the gas, it recovers, and there are no anatomical changes found when the animal is sacrificed. It follows, therefore, that changes which occur in animals subjected to chlorine and bromine derivatives of cyanogen are probably the result of the action of these halogen radicals.

PATHOLOGY OF CYANOGEN CHLORIDE POISONING

Cyanogen chloride has an action similar to hydrocyanic acid and causes death by paralysis of the respiratory center. Death may occur during exposure or within a few minutes thereafter. In the experiments of E. K. Marshall and E. J. Miller, there were no delayed deaths, and they say that if an animal survives 15 to 20 minutes after removal from the gas chamber, it will recover. The anatomical lesions found after exposure to cyanogen chloride may be best presented by an arbitrary division of the animals into three groups.

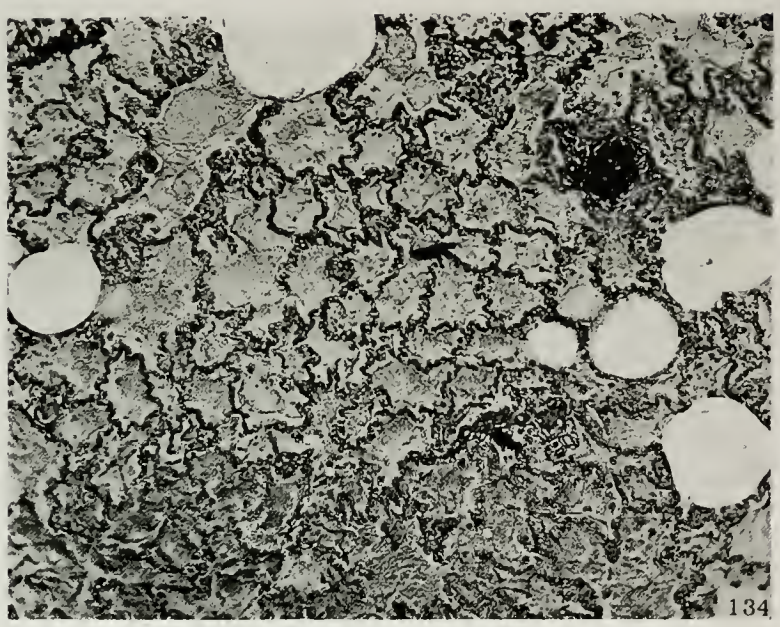

FIG. 2. SECTION OF LUNG SHOWING CONGESTION AND EDEMA IN A DOG DYING 8 HOURS AFTER EXPOSURE TO CYANOGEN CHLORIDE.

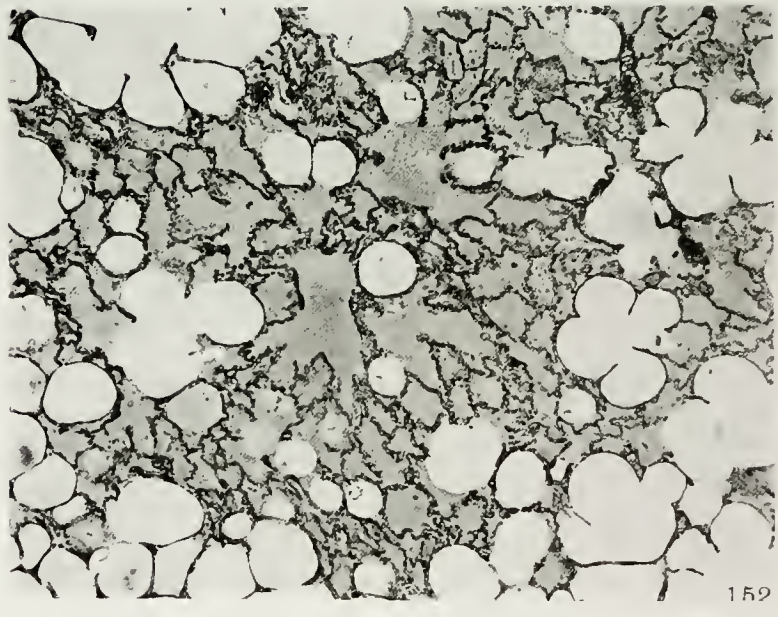

FIG. 4. SECTION OF LUNG SHOWING EDEMA AND EMPHYSEMA IN AN ANIMAL SURVIVING 30 HOURS AFTER EXPOSURE TO CYANOGEN BROMIDE.

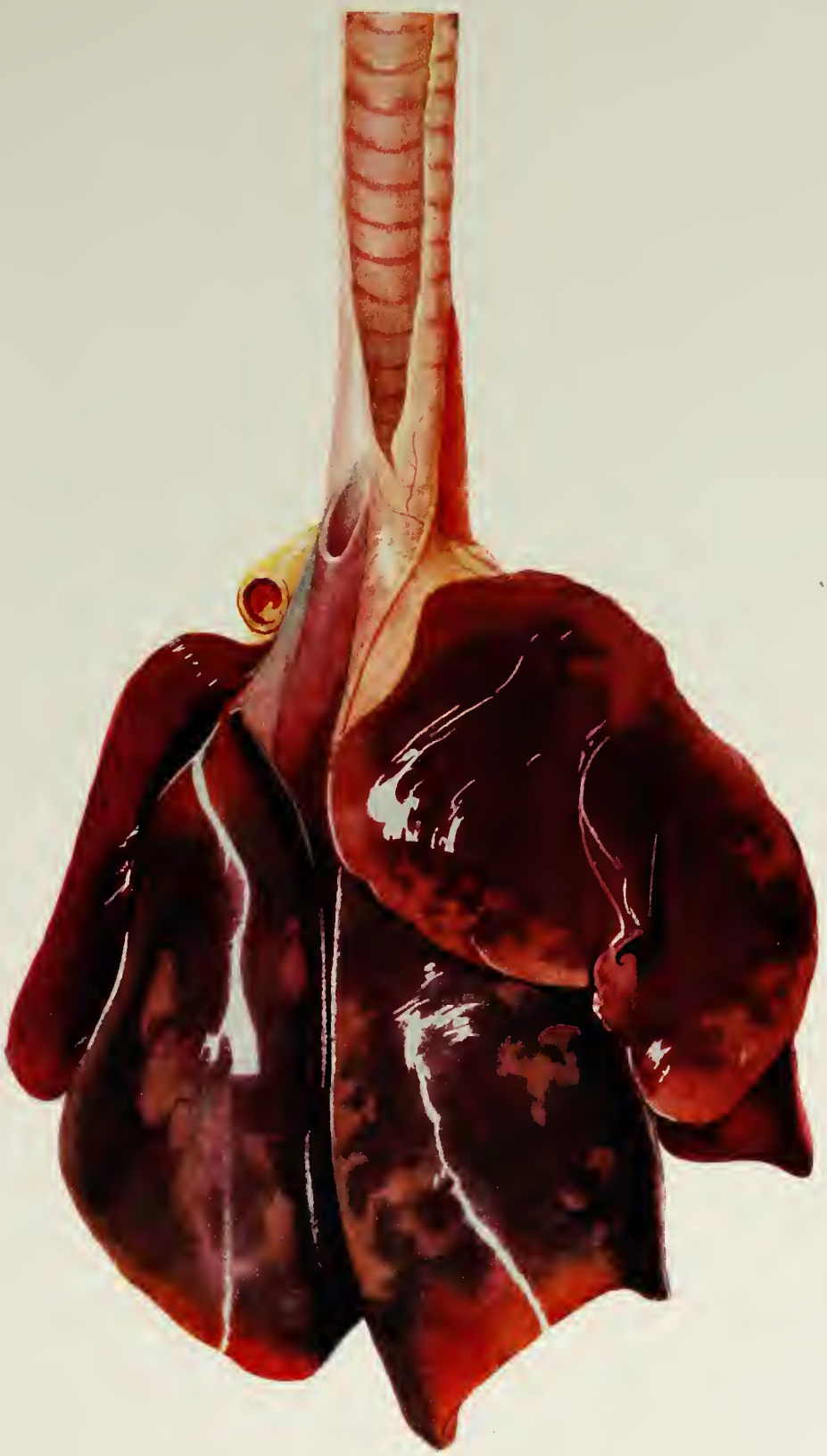

PLATE XXVIII

FIG. 3: LUNGS OF DOG SURVIVING 7 HOURS AFTER A LETHAL DOSE OF CYANOGEN BROMIDE.

GROUP I. *Animals that died in the gassing chamber or shortly thereafter.*

GROUP II. *Animals that were sacrificed 3 to 5 days after exposure to gas.*

GROUP III. *Animals that were sacrificed after a long interval up to two months after exposure to gas.*

GROUP I. *Animals That Died in the Gassing Chamber or Shortly Thereafter.*

Grossly, these animals present no striking abnormalities. The conjunctivæ may be slightly reddened. The chest is usually expanded, and the abdomen is scaphoid. On incision the blood flows freely from all vessels and is a bright cherry red. There is no marked splanchnic engorgement. The liver is purple. The pleural cavities contain no excess of fluid. The lungs are more voluminous than normal and the heart shows some right-sided dilation. Sub-epicardial and sub-endocardial hemorrhages may occur, but these are usually small and infrequent.

There is no abnormality of the upper respiratory tract. The trachea shows a pale white mucosa, and the small sub-mucous vessels stand out as a delicate red tracery. As the bronchi are approached, an excess of straw-colored fluid is encountered. The lungs are distinctly more voluminous and more firm than normal. They have a bright red color, (Fig. 1) and on section, an excess of fluid, rich in unclotted blood, escapes. This fluid is not increased by pressure on the lungs after the initial section. There is no evidence of an edematous sheath around the vessels. The other organs present nothing abnormal.

Histologically (Fig. 2), there is a pink-staining, granular material in the alveoli, and the bronchioles may contain small amounts of mucus in which cellular débris, including occasional red and white blood cells, is embedded. The alveoli vary slightly in size, and this is also true of the thickness of the alveolar walls. The other organs show no noteworthy deviation from the normal.

SUMMARY

The acute changes after exposure to cyanogen chloride are confined to pulmonary edema and congestion, associated with a very mild inflammatory process of the bronchioles. While the edema may be inconspicuous with minimal lethal doses, as the concentration is increased the edema is likewise augmented.

GROUP II. *Animals Sacrificed 3 to 5 Days After Exposure to the Gas.*

Grossly, except in the lungs, there is no deviation from the normal that could be ascribed to the action of the gas. In the lungs, which are not increased in size and which collapse on opening the thorax, there are occasionally small, red or reddish gray, slightly elevated, dry nodules to be seen both on the pleural surface and on section. The lung tissue in the neighborhood is pale pink. The larger bronchi have a pale mucosa, but in the smaller ones there is an increase of viscid cloudy material; such bronchioles may be the centers of the small nodules described above.

Histologically, there is again variation in the size of the alveoli and in the thickness of their walls. Groups of slightly atelectatic or emphysematous alveoli alternate throughout the section. In all probability this is associated with the inflammatory exudate found in the bronchioles. Here mucus, desquamated epithelial cells, as well as red and white blood cells in varying numbers, may occur. Such plugs may completely occlude the lumina of the bronchioles. The inflammatory process is most frequently confined to the bronchi-

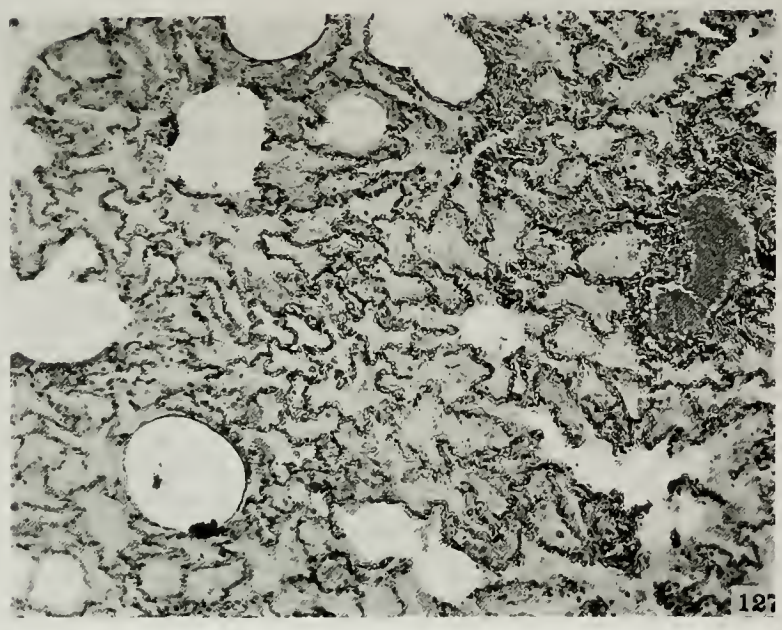

FIG. 5. SECTION OF LUNG SHOWING ENGORGEMENT OF CAPILLARIES AND EDEMA IN ACUTE STAGE IN A DOG DYING 2 HOURS AFTER EXPOSURE TO CYANOGEN BROMIDE.

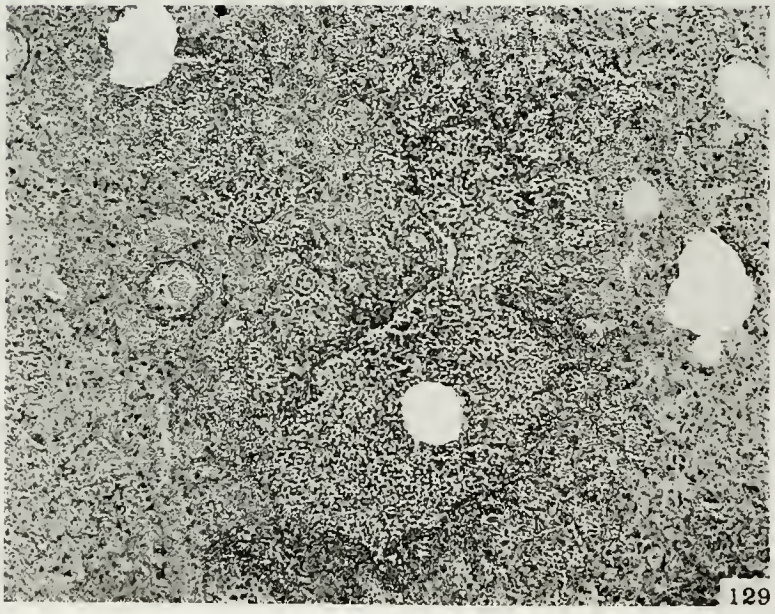

FIG. 6. SECTION OF LUNG SHOWING MARKED EDEMA AND INFILTRATION OF TISSUE BY POLYMORPHONUCLEAR LEUCOCYTES IN A DOG SURVIVING 4 DAYS.

oles as a mild catarrhal change, but occasionally it spreads to the neighboring alveoli to form localized broncho-pneumonic patches.

SUMMARY

Catarrhal bronchiolitis, associated with slight, localized vesicular emphysema or atelectasis and, rarely, with small patches of broncho-pneumonia, occurs after exposure to cyanogen chloride.

GROUP III. *Animals Sacrificed after a Long Interval up to Two Months After Exposure to the Gas.*

In this group, there are no gross anatomical lesions, and the histological changes are inconspicuous. Occasional bronchioles show a persistence of a catarrhal exudate similar to that described in Group II. They may also be distended and appear as sharp circles without any convolution to their walls. Occasionally, the submucosa and even the muscular coats may be the seat of mononuclear infiltration. The air vesicles vary considerably in size, and individual lobules are the seat of emphysema or collapse. In several animals focal pneumonic processes involving only a few alveoli were found, but in no instance was any organization of exudate encountered.

SUMMARY

The mild catarrhal inflammatory process in the bronchioles described in Group II may persist for a long period.

PATHOLOGY OF CYANOGEN BROMIDE POISONING

Cyanogen bromide differs somewhat in its action from the chlorine derivative. Although animals may die with a symptomatology not unlike that encountered in hydrocyanic acid poisoning, delayed death is common, and may occur hours or days after exposure.

The anatomical lesions found after exposure to the bromine derivative are very similar to those that occur after chlorine or phosgene gas, and may be divided, as in the case of these gases, in three groups:

GROUP I. *Animals that die within 36 hours after exposure to the gas.*
GROUP II. *Animals that die several days after exposure to the gas.*
GROUP III. *Animals sacrificed after a longer interval up to 4 weeks.*

GROUP I. *Animals That Die Within 36 hours After Exposure to the Gas.*

Grossly, there are no striking changes. The eyes may be reddened and the chest expanded. The abdomen, however, is not scaphoid. The blood does not clot rapidly, and marked splanchnic engorgement, with increased size of the liver, may be overlooked. The blood is usually bright red in these early cases. The pleural cavities may contain a slight excess of fluid. The voluminous lungs do not collapse and nearly meet in the median line. The heart is dilated, particularly on the right side. The blood in the heart may be fluid, and the cavities and valves present no marked abnormality, except for an occasional subendocardial hemorrhage. The tracheal mucosa is congested, and as early as half an hour after removal from the gas chamber, the lumen of the trachea, as well as those of all the bronchi, may be

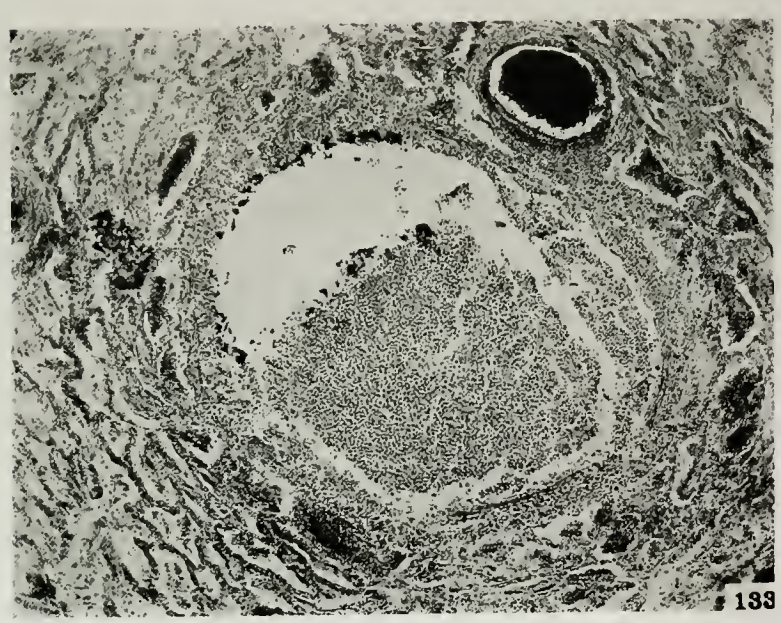

FIG. 7. SECTION OF LUNG SHOWING EXUDATE IN A BRONCHUS.

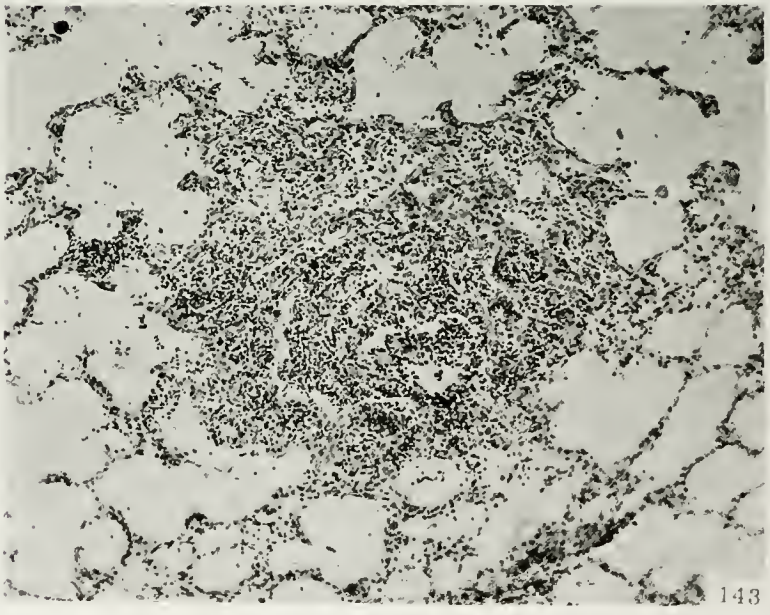

FIG. 8. SECTION OF LUNG SHOWING SMALL FOCUS OF BRONCHO-PNEUMONIA IN AN ANIMAL SURVIVING 2 MONTHS AFTER EXPOSURE TO CYANOGEN BROMIDE.

filled with a frothy, brownish fluid. The pleural surface of the heavy lung (Fig. 3) is very smooth and glistening, and the distended lymphatics, as well as the distended perivascular sheaths of the vessels at the hilus, are very prominent. The lympathic glands at the hilus are correspondingly swollen and succulent. On section, a large amount of fluid escapes from the lung tissue and on pressure the flow is greatly increased. Patches of bright red lung tissue alternate with paler pink areas, most prominent near the edges.

The other organs present no change aside from congestion.

Histologically, the trachea shows an exudate of mucus, some desquamation of the epithelium, which may occur in focal areas, and marked engorgement of the vessels of the submucosa. A similar exudate is found in the bronchi, and the bronchioles are frequently distended or irregularly contracted. Most frequently, the distention occurs in the ductus alveolaris (Fig. 4). The lung tissue is also the seat of considerable change. The alveoli contain an almost homogeneous, pink-staining material. The alveolar epithelium may be desquamated, and the blood vessels in the alveolar walls are distended with red blood (Fig. 5). They contain a greater percentage of polynuclear leucocytes than normally, and occasionally these have found their way into the lumen of the alveoli or may even be caught in process of migration. The liver shows marked engorgement of the central veins and of the neighboring capillaries so that the liver cells around the central vein are much more slender than normal. The congestion in the other viscera is not as marked, and aside from cloudy swelling, no noteworthy changes are encountered.

SUMMARY

Cyanogen bromide acts as an intense respiratory irritant, and produces an inflammatory exudate that extends throughout the bronchial ramifications into the pulmonary tissue. As early as half an hour after exposure to the gas, contraction and dilation of the bronchioles occur, and the lung is bathed in an inflammatory edema.

GROUP II. *Animals That Die 2 to 9 Days After Exposure to the Gas.*

The *external* appearance, as well as the picture of splanchnic engorgement described for Group I, persists. The heart is dilated, and the auricles contain large chicken fat clots. The musculature is firm, particularly on the left side, which is contracted frequently. The lungs are very voluminous, but in contrast to Group I, the increased volume is not always uniformly distributed. Entire lobes or parts of a lobe may be firm and non-air-containing, while other portions may show greatly distended alveoli and be very pale pink in contrast to the solid, dark, reddish purple areas. The lymphatics and the sheaths of the vessels at the hilus are still distended, and at times, the clear fluid within them may have given place to a bright pink fluid. The trachea contains frothy fluid, and a false, dull, yellowish gray membrane is found on the surface and remains as a covering even as far as the smaller bronchi. On section, the lungs show firm, maroon or grayish red areas, often wedge-shaped, involving, in the form of a lobar consolidation, an entire lobe or portions of many different lobes. Fluid escapes from the less firm areas, and in many instances, the dilated alveoli stand out prominently near the borders of the lungs.

Histologically, the trachea has lost its epithelial covering, and in its place, there is an exudate rich in fibrin, red and white blood cells, and desquamated epithelium. The blood vessels of the submucosa are dilated; the tissue of the submucosa is spread apart by the edema. Migrated leucocytes occasionally occur in this fluid. An exudate similar to that

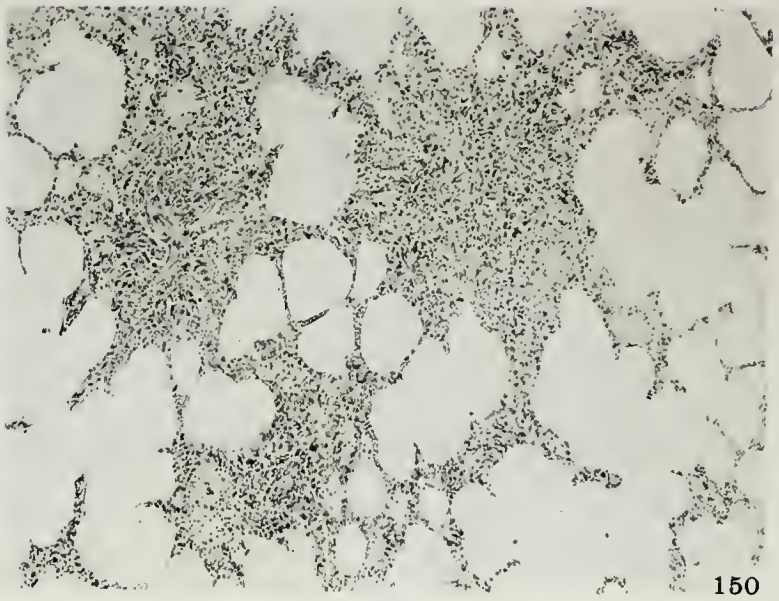

FIG. 9. SECTION OF LUNG SHOWING SMALL AREAS OF ORGANIZATION IN ANIMAL SURVIVING 2 MONTHS AFTER EXPOSURE TO CYANOGEN BROMIDE.

in the trachea is found in the bronchi and especially in the finer bronchioles. Not infrequently, the wall of the bronchiole and the walls of the surrounding alveoli are stained a uniform pink and are overshadowed by a mass of polynuclear leucocytes that form a minute abscess in the place of the necrotic bronchiolar and alveolar walls (Figs. 6 and 7). Between such areas the alveoli contain a more typical pneumonic exudate, which may vary even to the mildest grade and consist largely of pink-staining serum with only a few cells and little fibrin.

The other organs show only mild parenchymatous changes and congestion.

SUMMARY

The inflammatory reaction encountered in Group I progresses in those animals that survive for several (2 to 9) days, to produce extensive lobular pneumonia, which is often associated with a necrotizing process in the bronchiolar and lung tissues.

GROUP III. *Animals Sacrificed After a Longer Interval up to 4 Weeks After Exposure to the Gas.*

In this group there are no marked *external* changes. The splanchnic engorgement is not present. The lungs are not markedly increased in volume, and the heart is not constantly either distended or contracted. The upper respiratory tract shows only a mild inflammatory process, and, frequently, the trachea may be quite pale and its epithelium delicate. As the smaller bronchi are reached, however, some of them show exudate which is muco-purulent in character. The lungs are for the most part air-containing, but slightly depressed, dark, reddish brown patches occur. These are often wedge-shaped with their bases at the margin of a lobe. They are in sharp contrast to the pale, pinkish lung tissue which surrounds them. These areas of consolidation vary greatly in size and number. On section, they have a typical appearance: brown or red, elevated, non-air-containing, and often with a central core of muco-purulent material.

Histologically, the striking change is in the bronchi. Their walls are greatly thickened, and the lumina may be dilated and contain a mass of mucus and cellular débris in which there are many polynuclear leucocytes (Fig. 8). Their epithelium is quite low, metaplastic, or lacking. Their walls are infiltrated with mononuclear cells. The surrounding alveoli are often either compressed or emphysematous. In still other areas, the alveoli contain an exudate. This is sometimes composed of irregular polyhedral cells, probably desquamated alveolar wall cells, but not infrequently a more typical pneumonic exudate in process of organization occurs (Figs. 9, and 10).

SUMMARY

Animals that have been exposed to cyanogen bromide but do not succumb acutely have a persistence of an infection in the respiratory tract. This is characterized by bronchiolectasis and purulent bronchiolitis, associated with changes in the size of the alveoli and with an organization of the inflammatory exudate.

CONCLUSIONS

Cyanogen chloride produces a mild irritation of the respiratory tract.

Cyanogen bromide, however, produces a severe inflammatory reaction analogous to that of chlorine gas. This irritative action must be attributed to the halogen radical, since hydrocyanic acid itself has no direct effect on the respiratory tract.

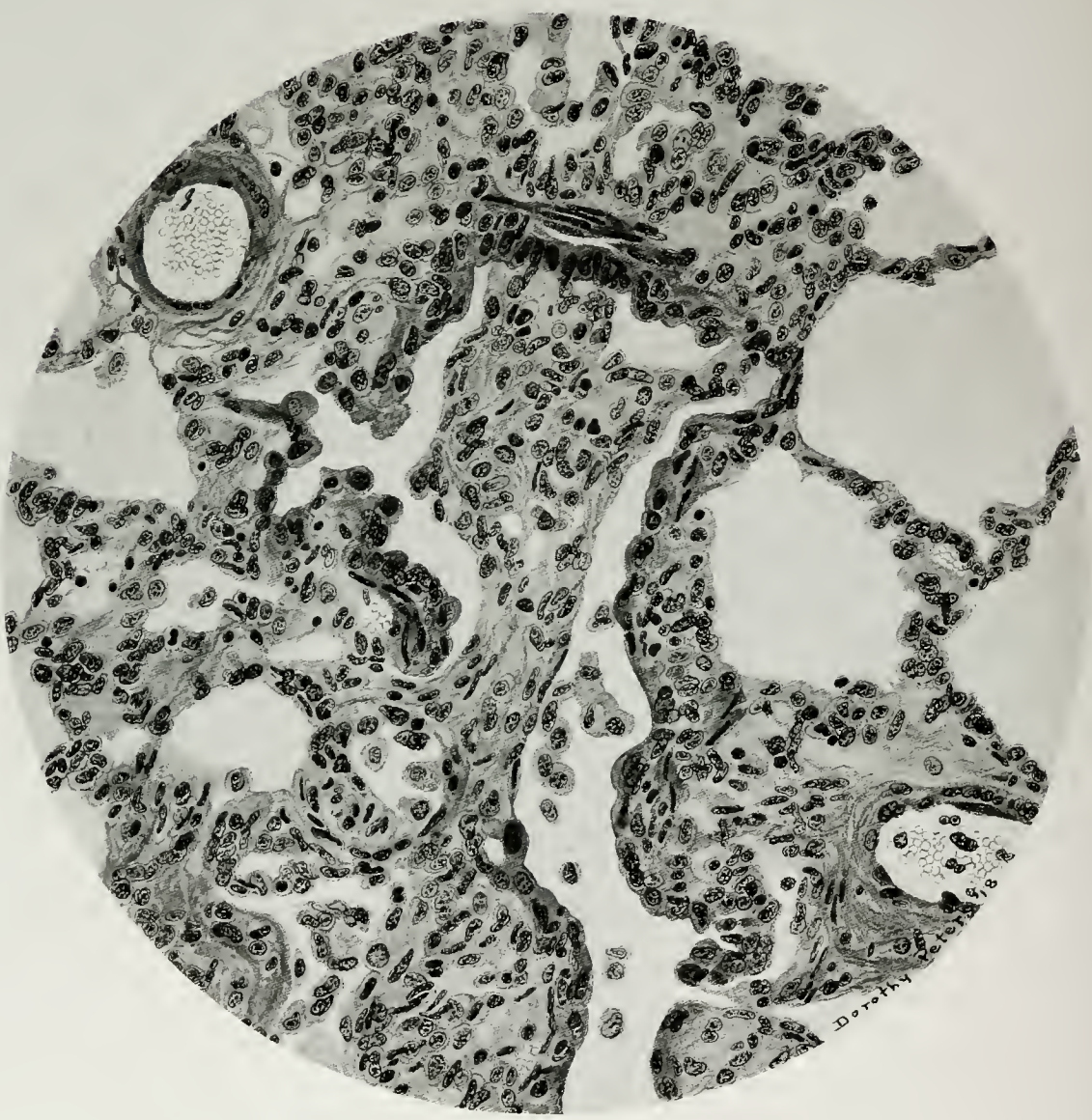

FIG. 10. DRAWING OF SECTION OF LUNG SHOWING ORGANIZATION IN A BRONCHIOLE IN A DOG SURVIVING 2 MONTHS AFTER EXPOSURE TO CYANOGEN BROMIDE.

THE PATHOLOGY OF POISONING BY ARSINE

BY

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PLATE XXIX

FIG. 1: SPLEEN, KIDNEY, AND WALL OF AORTA FROM A DOG DYING 8 HOURS AFTER INHALATION OF ARSINE. THEY SHOW THE TREMENDOUS SIZE OF THE SPLEEN AND THE CHARACTERISTIC COLOR DUE TO HEMOLYSIS, SEEN IN ALL THE TISSUES AFTER ACUTE POISONING BY ARSINE.

THE PATHOLOGY OF POISONING BY ARSINE

INTRODUCTION

Arsine (AsH_3), or arseniuretted hydrogen, has aroused considerable medical interest because fatal accidents from the gas in industrial pursuits have been reported. The gas is singularly interesting since it differs in its action upon the tissues from all other arsenic compounds. It possesses a marked affinity for hemoglobin, which results in hemolysis of the red blood corpuscles, accompanied by severe symptoms and manifests itself as icterus and hemoglobinuria.

During exposure to arsine in the gassing chamber, dogs very rarely show any symptoms. One to two hours after exposure to lethal concentrations of the gas they become very depressed, shivering develops, and, finally, they pass into a state of complete prostration, which lasts until death. The urine voided after 6 to 12 hours is bloody. The scleræ at first are a diffuse, dusky red, becoming yellow with the gradual onset of jaundice. Animals which survive are usually depressed for a period of days or weeks, show loss of appetite, and considerable emaciation. Hemoglobinuria persists for some days.

The mechanism of hemolysis from arsine has been studied by a number of observers. They all note the presence of free hemoglobin in the blood stream, although there is some divergence of opinion as to how arsine acts upon and liberates the hemoglobin from the blood corpuscles. Arsine is a strong reducing agent, and Naunyn (1) showed by experiments *in vitro* that hemolysis never occurs in the absence of oxygen. Meissner (2) believes that arsine within a short period after entry into the body is either oxidized by the hemoglobin within the corpuscle or enters into a complex combination with it. He thinks that the hematin radical is mainly responsible for the reaction. This he considers as the first phase of hemolysis. The second phase occupies a period of several hours, referred to by some authors as the latent period, and finally terminates in the rupture of the corpuscle. Mackenzie (3), from some experiments upon the nature of the hemolysis, arrives at the following conclusions: "Upon entering the blood stream, arsine is taken up by the hemoglobin of the red blood corpuscles, forming a compound which imparts a brownish color to the blood. In the presence of the oxygen in the corpuscles the arsenic hemoglobin compound is gradually converted into arsenic oxide, and during this process of oxidation, hemolysis takes place."

With the onset of hemolysis, a very marked secondary anemia develops. The hemoglobin readings fall within several days to 20 per cent. or below. The erythrocyte counts not uncommonly sink within seventy-two hours to between one and two million cells. In stained specimens, many of the red blood cells show basophilic stippling, poikilocytosis, and anisocytosis. Bone marrow stimulation is evidenced by the appearance in the circulation of numerous normoblasts, and a few megaloblasts. A moderate increase in polymorphonuclear neutrophilic leucocytes often occurs.

The following report is based upon the study of the pathological findings in 50 dogs which were poisoned with arsine by inhalation.

For convenience in describing the pathological lesions found at autopsy, the animals examined are divided into three groups.

GROUP I. *Animals dying acutely within twelve hours after exposure in which hemolysis is the main pathological finding.*

GROUP II. *Animals dying after twelve hours in which, in addition to hemolysis, icterus has developed.*

GROUP III. *Animals which survive and are killed after partial or complete recovery.*

It must be understood that there is no sharp dividing line between Groups I and II; but there are so many animals dying acutely which exhibit practically no jaundice, and others which show a profound icterus, which nearly masks the former condition, that it seems advisable to make an arbitrary division.

GROUP I. *Animals Dying Acutely Within Twelve Hours After Exposure in Which Hemolysis is the Main Pathological Finding.*

Externally, these animals show nothing striking. The scleræ are a diffuse purple. The mucous surfaces and subcutaneous tissues have a dull, rusty tint. The surfaces of the serous cavities exhibit a discoloration, which resembles very much that accompanying post-mortem decomposition. The pleural cavities occasionally contain an excess of hemoglobin-tinged fluid. The lungs and trachea, beyond partaking of the same color as the other tissues, appear normal. Now and then they seem slightly edematous.

The blood in heart and vessels is fluid. The staining due to hemolysis is nowhere more strikingly shown than in the arterial walls (Fig. 1).

On examining the abdominal viscera, one is at once struck by the appearance of the spleen (Fig. 1). It is usually two or three times its normal size, with a shiny, glistening capsule. Its color is deep purple. On section the organ seems somewhat congested and edematous. The Malpighian bodies are poorly defined.

The liver at this stage is normal in shape and size. It is somewhat chocolate-colored and in some instances quite brown.

The stomach and intestines are characteristically discolored by hemoglobin but otherwise normal.

The kidneys immediately attract attention (Fig. 1). Their surfaces are a very dark red of uniform intensity. The capsules strip readily. On section, the same garnet red shade is encountered, of such intensity that little detail can be made out. The boundary zone of Henle stands out, however, as a red band, darker than the rest of the kidney. The bladder contains as a rule an excess of deeply blood-tinged urine. The suprarenal glands appear normal.

Urine examination reveals the presence of large quantities of oxy- and methemoglobin, both of which give a characteristic spectrum. Occasionally, red blood cells are encountered. Albumin is frequently present.

The spleen, liver, and kidneys are the only tissues of *microscopic* interest. One finds the splenic sinuses distended with an enormous quantity of disintegrating erythrocytes and finely granular débris. There is also considerable activity shown by the large mononuclear phagocytes composing the reticulum and lining the sinuses.

The picture in the liver is analogous to that in the spleen. The sinuses here contain

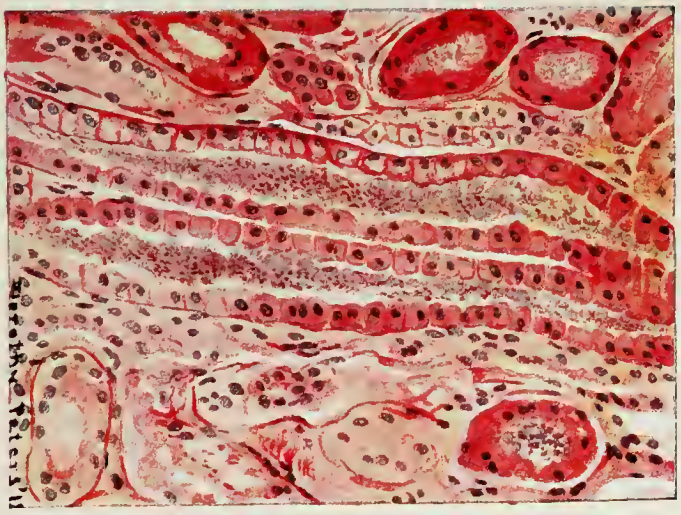

PLATE XXX

FIG. 2: SECTION OF KIDNEY OF DOG SUCCUMBING AFTER 10 HOURS TO A LETHAL DOSE OF ARSINE. THE RENAL TUBULES CONTAIN QUANTITIES OF BROWNISH METHEMOGLOBIN.

many disintegrating red blood cells. The Kupffer cells are actively engaged in phagocytizing the moribund and fragmented cells.

Bowman's capsules and the renal tubules are filled with a loosely packed, reddish, amorphous, finely granular débris. This material is largely methemoglobin, which the kidneys are in the act of excreting (Fig. 2).

The renal epithelium is quite normal.

SUMMARY

Arsine is an intense hemolytic agent. Its action manifests itself, after a latent period of 4 to 6 hours, in the production of hemoglobinemia and severe hemoglobinuria.

GROUP II. *Animals Dying After 12 Hours in Which Icterus Predominates.*

In the first group the pathological lesions in animals dying acutely from hemolysis were described. Animals which survive this period become very jaundiced and present a striking pathological picture.

It may be recalled that the body converts disintegrated red blood cells into bile and so rids itself of the waste products, or possibly converts them into substances that are again assimilable. When by a sudden destruction of erythrocytes, this mechanism is over-taxed, bile is formed in excess of the rate at which it can be excreted, and jaundice results. The classic experiments of Minkowski and Naunyn (4) demonstrated that the liver is responsible for the conversion of hemoglobin into bile, for when they removed the livers of geese previous to gassing by arsine, hemolysis occurred but icterus did not result.

The skin, scleræ, mucous surfaces, and subcutaneous tissues of the animals in this group are invariably jaundiced. The serous surfaces and internal organs have a pronounced yellow color. The blood frequently is brownish and always remains fluid in the heart and vessels. The arterial walls are deeply jaundiced (Fig. 3).

The spleen is not nearly as large as during the period of acute hemolysis and, instead of a deep purple, now it has become a dull brick red (Fig. 3). The liver is reddish yellow, large, and flabby. On section, it presents a fatty appearance; there is no excess of blood in the vessels. Tiny droplets of bile exude from the distended canaliculi. The gall bladder is conspicuous, and contains a large quantity of light brown, syrupy bile.

The small intestine contains an abnormally large amount of bile.

The kidneys are large and blue black in color (Fig. 3). The capsule strips readily, leaving a surface which varies somewhat in color in different animals. Frequently, it is a very deep brown or orange, but at other times, it is almost black, either uniformly so or mottled. On section the same colors are seen. A dark band in the boundary zone of Henle is always present, and the cortex is often traversed by dark-colored striæ (Fig. 4).

In the spleen, *microscopically*, one encounters less cell débris in the sinuses than in the more acute stage. Macrophages, heavily laden with detritus and iron-containing pigment, abound. Similar inclusion of pigment by the Kupffer cells in the liver is noted. Both the Kupffer cells and the liver parenchyma give a marked reaction for iron. In the liver cells, the reaction is most pronounced in the portion of the cell adjacent to the bile canaliculi (Fig 5).

The renal tubules are filled with brownish, granular, or, oftentimes, crystalline deposits of methemoglobin. This substance may become so tightly packed together in the tubules that casts are formed, and are passed in the urine. Anuria may result from complete

occlusion of the tubules. Resorption of methemoglobin by the epithelium lining the tubules occurs, with the subsequent deposition of iron-containing pigment.

The bladder contains reddish brown urine in which methemoglobin predominates in amorphous or crystalline form. Red blood cells, casts, and albumin are occasionally found.

SUMMARY

Hemolysis manifests itself further in the development of icterus, from which all the tissues become jaundiced; and changes occur in the liver and spleen. Hemoglobinuria persists.

GROUP III. *Animals Which Survive and are Killed After Partial or Complete Recovery.*

After 4 to 6 days, the jaundice, which is so characteristic of the second stage, fades The hemoglobinuria ceases; the viscera lose their icteric tint, but for some time possess an abnormal pallor, attributable to the anemia from loss of blood.

The red cell counts and hemoglobin estimations gradually rise. Evidence of the stimulation of the hemopoietic function is seen in the presence of immature erythroblasts in the peripheral circulation. Microscopically, the bone marrow is found slightly hyperplastic, showing numerous erythroblasts in all stages of development.

Liver and spleen show no trace of their former condition beyond, under the microscope, the presence of pigment granules in mononuclear phagocytes.

The kidneys do not appear to have been severely damaged, for every trace of the methemoglobin disappears, and the injured tubules are restored to normal. Deposits of hemosiderin are encountered for some time.

SUMMARY

Hemoglobinuria ceases after 2 to 4 days. The jaundice disappears at the end of a week. Secondary anemia persists for a period of days. There are no permanent lesions discoverable after poisoning by arsine.

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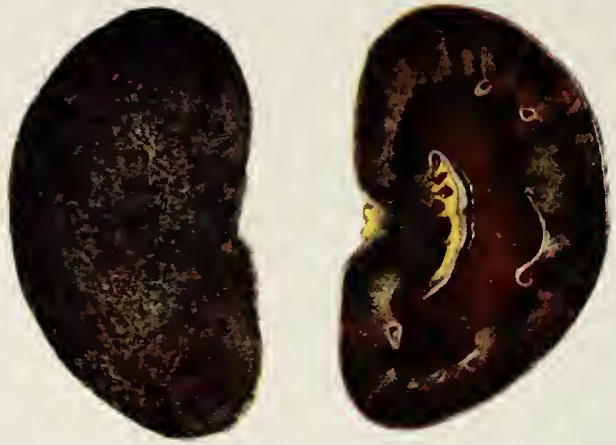
PLATE XXXI

FIG. 3: SPLEEN, KIDNEY, AND SECTION OF AORTA OF DOG SURVIVING 49 HOURS AFTER INHALATION OF ARSINE. THEY SHOW THE CHARACTERISTIC APPEARANCE DURING THE STAGE OF INTENSE JAUNDICE.



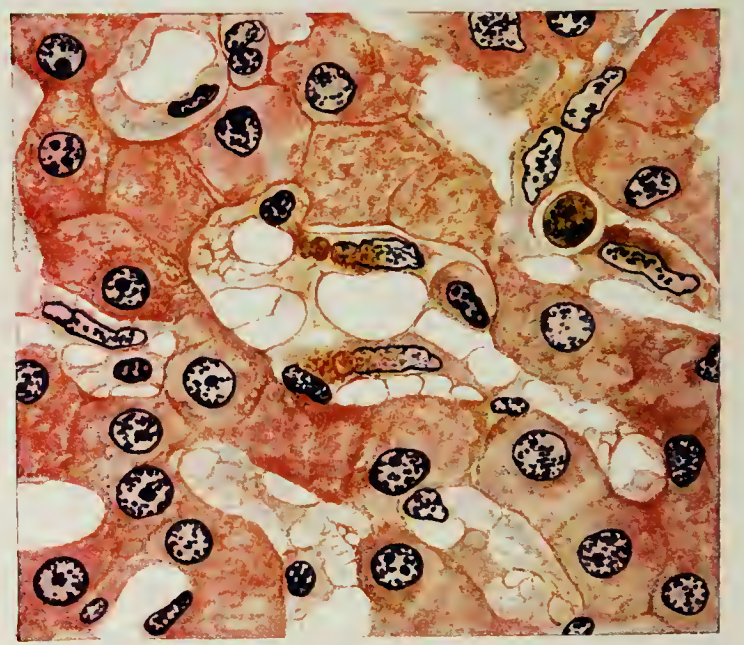


PLATE XXXII

FIG. 4. KIDNEY OF DOG. DEATH OCCURRED IN 5 DAYS AFTER EXPOSURE TO ARSINE. THE SURFACE IS MOTTLED AND DARK. ON SECTION THE DARK STRIAE IN THE CORTEX ARE PLAINLY VISIBLE.

FIG. 5. SECTION OF LIVER OF DOG DYING 2 DAYS AFTER EXPOSURE TO A LETHAL DOSE OF ARSINE. THE KUPFFER CELLS ARE LADEN WITH PIGMENT IN THEIR CYTOPLASM.

THE PATHOLOGY OF POISONING BY ORGANIC ARSENIC COMPOUNDS

BY

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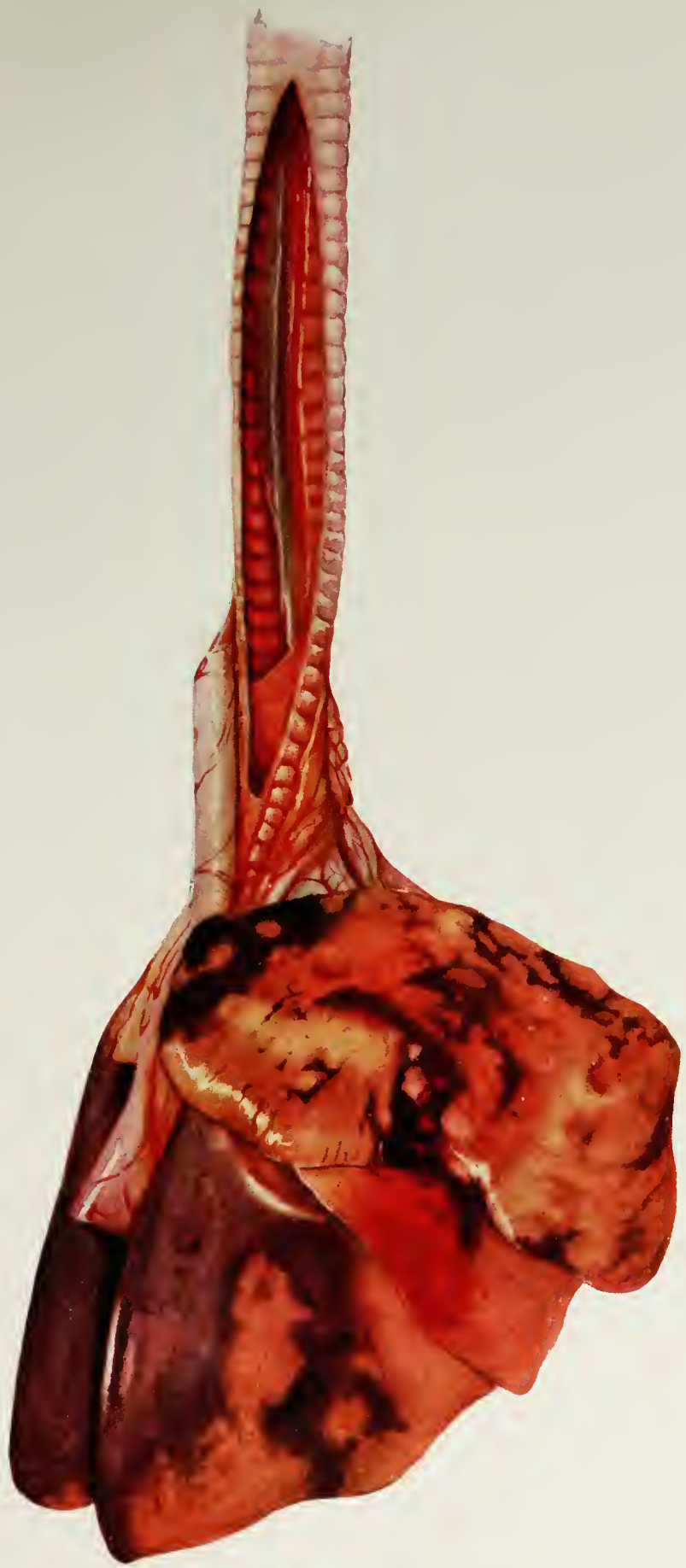


PLATE XXXIII

FIG. 1: TRACHEA AND LUNGS FROM DOG DYING ONE DAY AFTER EXPOSURE TO ETHYL-DICHLOR-ARSINE. INTENSE CONGESTION OF TRACHEA WITH MEMBRANE, CONGESTION AND EDEMA OF LUNGS.

THE PATHOLOGY OF POISONING BY ORGANIC ARSENIC COMPOUNDS

In this report the findings are presented of the study of the pathological lesions found in dogs which had been exposed to various concentrations of three organic arsenic compounds, namely, methyl-, ethyl-, and phenyl-, dichlor-arsine.

I. METHYL–DICHLOR–ARSINE

Dogs which have been exposed to this gas fall naturally into three main groups: (I) those which die acutely within a few hours to two days after exposure and show acute changes in the respiratory tract; (II) those which die two days to two weeks after exposure as a result of pneumonia; and (III) those which survive the exposure, recover their former state of health and die after a long period or are killed for autopsy.

Occasionally, lesions of the eyes are found, and, occasionally, erythematous patches on the skin, but these lesions are not severe or constant enough to serve as a basis of pathological grouping.

GROUP I. *Dogs Which Die Acutely.*

After exposure to high concentrations, death may occur within four hours, but rarely occurs before 18 to 24 hours. The symptomatology during this acute period may be briefly summarized. While in the gassing chamber, the dogs show signs of marked irritation and often become excited. There is profuse lachrymation, salivation, and nasal discharge, accompanied by sneezing and often by retching and vomiting. After removal from the chamber, the animals are depressed, have no appetite, and begin to exhibit more or less respiratory distress. Vomiting is frequent, and diarrhea may be present. After a few hours, wheezing and râles may be heard, and the rate of respiration is increased. The pulse becomes rapid and feeble as the respiratory signs are augmented, the animal becomes semicomatose, and dies in collapse.

The pathological findings in these acute animals are as follows:

The *conjunctivæ* are reddened and congested; there is often a frothy discharge from nose and mouth; the skin of the groins where sparsely covered by hair frequently shows red patches extending throughout the thickness of the corium.

On opening the *thorax*, the lungs are voluminous, nearly filling the chest. All lobes usually share equally in the increase in size and other changes. The pleural surfaces are moist, without the presence of free fluid in the pleural cavities. The surfaces are smooth, bright red in color, with more or less mottling over the surfaces, caused by alternating groups of air-containing and serum-containing alveoli (Fig. 1). On removing the lungs, they are felt to be heavy, and the lobes retain their shape well, although hanging in a sodden mass from the hilus. On section, the cut surfaces drip frothy pink fluid mixed with blood.

The color is not uniform, but areas of darker red appear here and there throughout the lungs. These areas are often firmer in consistency than the more normal spongy tissue, and give the impression of jelly which has begun to set. The anterior tips of the middle and upper lobes most frequently show these dark red areas.

The *bronchi* are usually not conspicuous on the cut surface of the lung, though they may be filled with tenacious fibrinous plugs. The trachea, however, shows a striking false membrane throughout its entire length (Fig. 1). The membrane is quite thick and edematous, sometimes quite white in color, in contrast to the walls of the trachea, which are congested and often intensely red. More frequently, the membrane is stained pink by the frothy fluid which pours up from the lungs. In the earliest stages the membrane can usually be stripped entire from the surface beneath; later on it loses its tough, elastic quality, becomes yellowish, softer, heavier, and, finally, purulent and necrotic. The surface beneath is red, raw, and, occasionally, small bleeding points can be seen. The larynx, up to the vocal cords, shows a continuation of the membrane; above this point, the congestion and edema of the mucosa is still present, but usually the membrane is lacking. The formation of this membrane takes place quickly and has been found in dogs dying as early as 4 hours after exposure. In many of these extremely acute dogs, there is no membrane, but instead congestion and some edema of the mucosa. In dogs dying at the end of the second day or later, the membrane is replaced by thick purulent exudate.

The *heart* is dilated and is filled with dark red, almost black post-mortem clot, particularly on the right side. The pericardial fluid is not increased in amount and is not bloody.

The *abdominal viscera* may show moderate degrees of congestion, but this is never a striking feature. The liver is firm and dark red. The spleen varies considerably, but is usually slightly swollen, presenting a smooth, soft surface; on section, its Malpighian bodies are not conspicuous. The kidneys present a smooth surface, a dark red cortex, with usually a lighter pyramid, and no marked abnormalities. The adrenals look entirely normal on the surface; but on section, the medulla is usually markedly congested, and, occasionally, pin-point hemorrhages can be seen at the line of juncture of cortex with medulla. The intestines show nothing of especial interest; the mucous surfaces are not congested. The urine found in the bladder has its normal yellow color.

Microscopically, the only changes of importance are in the respiratory tract. The membrane in the trachea is found to consist of a fibrin network with large spaces full of edematous fluid. The epithelial lining of the trachea has been lifted off, and in some cases, can be seen as a ragged line floating out through the edematous fibrin (Fig. 2). In the early stages, there is but little polymorphonuclear infiltration; but this becomes more marked in a short time, and the membrane may stain a dusky purple because of the presence of pyknotic nuclei of leucocytes. The submucosa also shows some leucocytic infiltration, but this never becomes extreme, and many of the leucocytes are mononuclear; the edema of the submucosa is also of a moderate degree. Sometimes the inflammatory process extends beyond the cartilaginous rings. Later on the membrane becomes a dense mass of necrotic purple-staining material, which lies upon the submucosa, with no intervening epithelial layer. It may be noticed in many cases that while the epithelium is completely denuded over the greater part of the circumference of the trachea, it is still intact over the posterior portion, that part which is not surrounded by cartilage.

In the lungs the microscopical changes are principally those associated with the congestion and edema seen in the gross. The edema is rarely of even distribution throughout the section, but groups of alveoli are seen filled with pink-staining, homogeneous material

PLATE XXXIV

FIG. 2: TRACHEA WITH EDEMATOUS MEMBRANE IN DOG DYING 19 HOURS AFTER EXPOSURE TO PHENYL-DICHLOR-ARSINE.

PLATE XXXV

FIG. 3: GREAT CONGESTION OF CAPILLARIES IN ALVEOLAR WALLS AND EDEMA FLUID IN ALVEOLI. BRONCHIAL EPITHELIUM PRACTICALLY UNINJURED. DEATH IN ONE DAY.

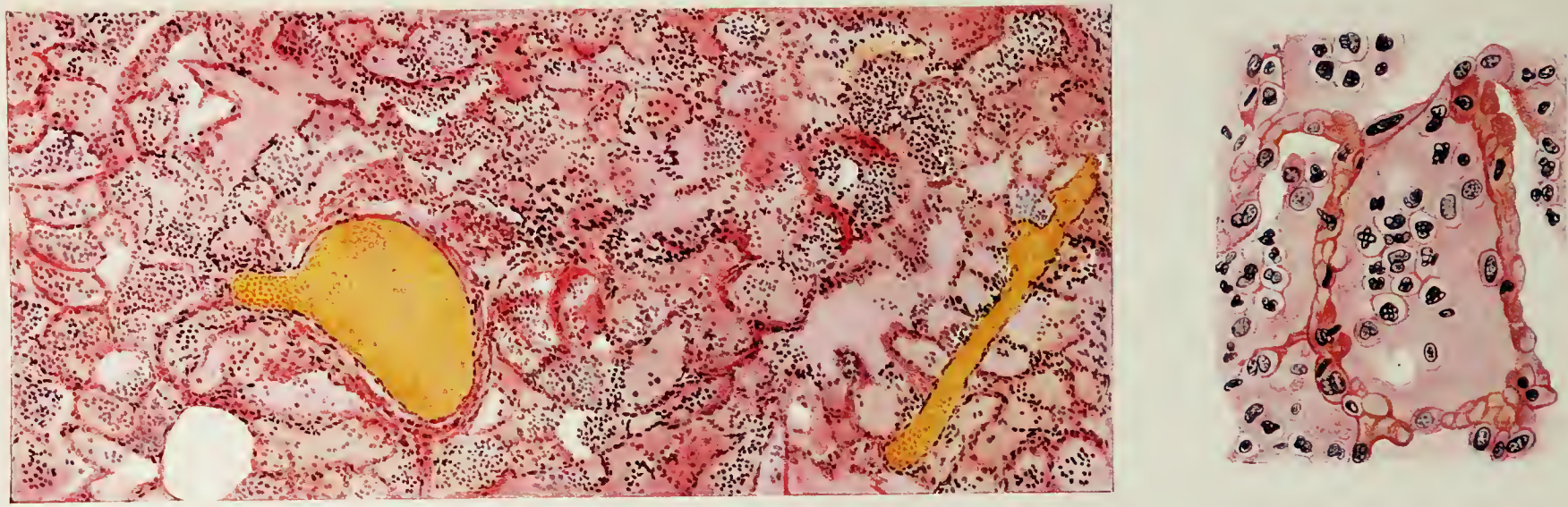


PLATE XXXVI

FIG. 4: PNEUMONIA ARISING DIFFUSELY THROUGHOUT TISSUE FULL OF EDEMA. SMALL ENLARGEMENT SHOWS DESQUAMATION OF ALVEOLAR CELLS AS WELL AS SLIGHT LEUCOCYTIC INFILTRATION.

adjacent to other groups of alveoli over-distended with air (Fig. 3). This corresponds to the mottled appearance presented by the surfaces of the lungs. The capillaries of the alveolar walls, particularly in the edematous areas, are tortuous and filled with red blood cells (Fig. 3). The alveolar epithelium seems to have suffered little, and is in most places intact; where the edema is most marked, there is more or less desquamation, and swollen round cells are found floating in the fluid. In places much fibrin can be seen in the edematous alveoli. The bronchi show a continuation of the tracheal membrane in a milder degree, and the bronchioles usually present an intact epithelium. Frequently, there is marked peribronchial and perivascular edema.

Microscopical changes in the other organs are of minor degree, and consist of slight swelling and granulation of cells in the liver and kidneys, and of congestion of the vessels of the adrenal medulla, with occasional minute hemorrhages.

GROUP II. *Dogs Which Die from Pneumonia 2 Days to 2 Weeks After Exposure.*

The dogs of this group show more variation than those of the first group. Those which die in two or three days show a persistence of the acute conditions described above, upon which is superimposed a beginning pneumonia. Those which die toward the end of the two-week period show little trace of the original conditions, but have extensive pneumonia of various types.

It appears from a study of the microscopical sections that the pneumonia may develop in two ways. First, the extensive edema of the acute stage may become diffusely infiltrated with polmorphonuclear leucocytes, and the edema may change to a cellular exudate over large areas of lung, bearing little direct anatomical relationship to the bronchi (Fig. 4). Second, the smaller bronchi and bronchioles may become ringed with leucocytes, their epithelium degenerated, their walls infiltrated, and each bronchiole the center of a small focus or nodule of pneumonic consolidation (Fig. 5).

In the first case, the consolidated area may occupy all of a lobe or several lobes, and the lungs retain a heavy, wet consistency. In the second case, the areas involved are practically always the anterior tips of the middle and upper lobes, while the posterior portions of these lobes and the whole of the lower lobes present an air-containing and emphysematous condition, sometimes with slight congestion, sometimes with none.

The pneumonias are of different types: some are soft, wet, and purulent, with the bronchi containing streams of purulent material; others are firm, gray, solid pneumonias; still others are red with many small discrete gray nodules standing out on the cut surface.

In dogs which have lived for some time after the development of pneumonia, abscesses may be found, with fibrino-purulent pleurisy (Figs. 6 and 7). The acute conjunctivitis of the early stage subsides and rarely develops into a purulent discharge. Ulceration of the cornea has been found in only one or two isolated cases. The skin lesions also subside without ulceration, blistering, or sloughing.

GROUP III. *Dogs Which Survive for Long Periods.*

Some dogs which have survived for 3 weeks or more after exposure have died with acute pneumonia of only a few days' duration. Others have died with extensive purulent pleurisy or empyema. There seems to be no definite proof that these animals developed this condition as a result of exposure to the gas, as we have had animals come to autopsy with the same lesions before exposure to any gas.

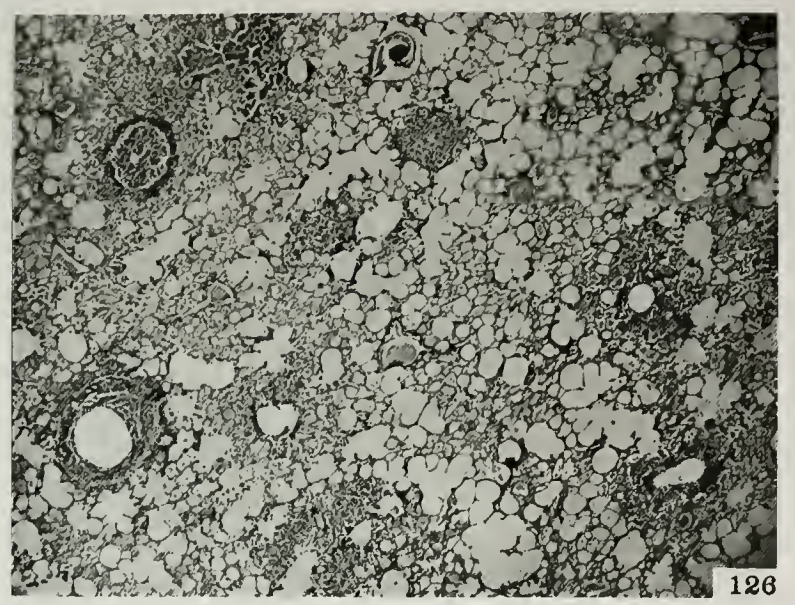


FIG. 5. PNEUMONIA BEGINNING AS SMALL DISCRETE NODULES AROUND BRONCHIOLES WHICH CONTAIN PLUGS OF EXUDATE.

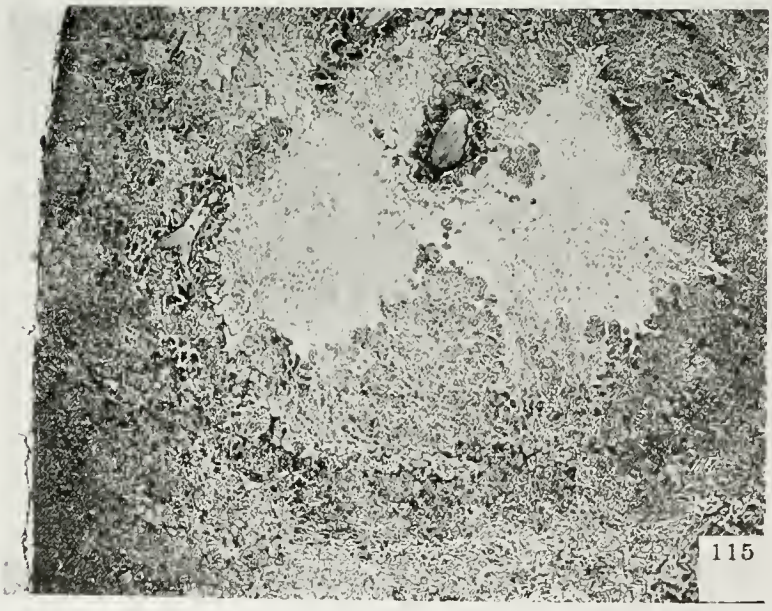


FIG. 7. MICRO-PHOTOGRAPH OF SMALL ABSCESS IN LUNG OF DOG DYING 10 DAYS AFTER EXPOSURE.

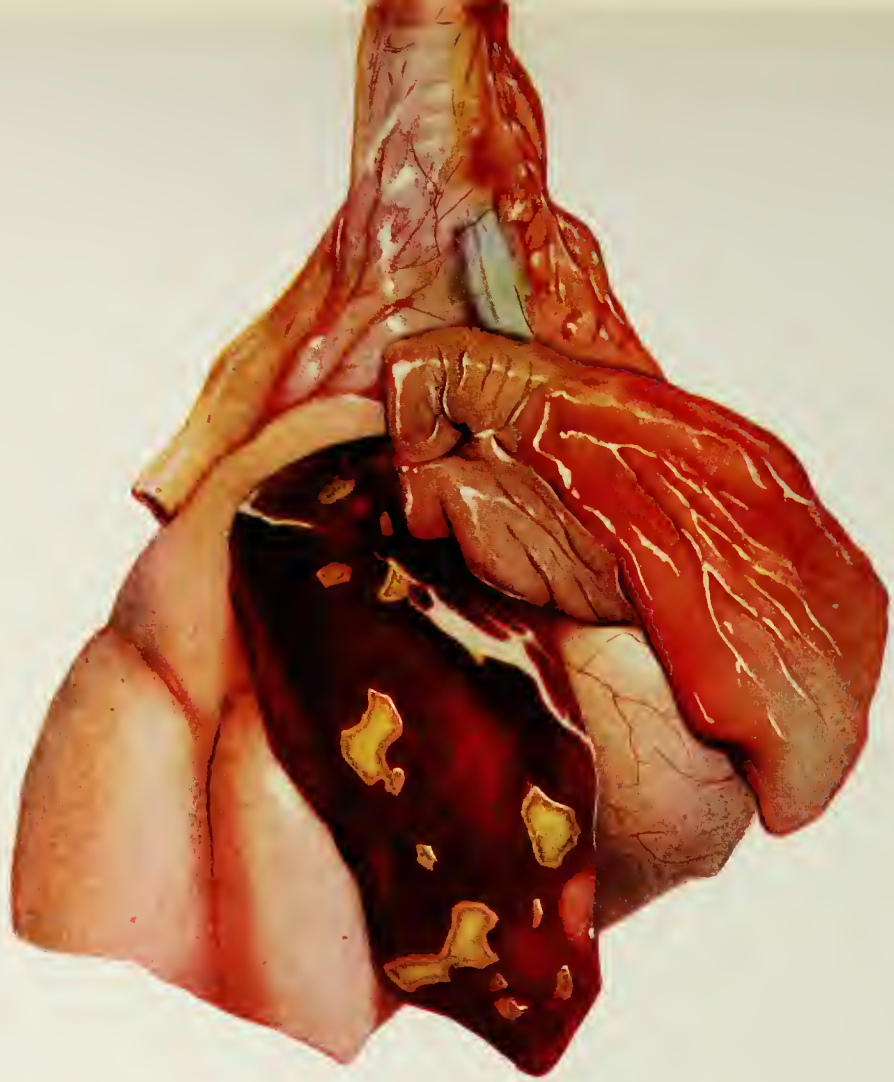


PLATE XXXVII

FIG. 6: PNEUMONIA CONFINED TO ONE LOBE AND APPEARING AS LARGE YELLOW ABSCESSES ON THE SURFACE IN DOG DYING 5 DAYS AFTER EXPOSURE.

PLATE XXXVIII

FIGS. 8, 9: CONGESTION AND HEMORRHAGE ABOUT THE BRONCHIAL TREE STANDING OUT SHARPLY AGAINST RELATIVELY NORMAL LUNG TISSUE. DOGS DYING ABOUT 24 HOURS AFTER EXPOSURE TO ETHYL-DICHLOR-ARSINE.

Those dogs which survived for long periods and were sacrificed for autopsy have shown no gross anatomical lesions. Microscopically, no changes have been found in the lungs or bronchioles, (in the trachea there is sometimes evidence that the epithelium has not recovered its normal thickness or structure).

II. ETHYL–DICHLOR–ARSINE

Dogs exposed to this gas fall into the same groups as have been outlined above; but there is a far greater proportion of acute deaths with the ethyl- than with the methyl-compound, although the range of variation in concentration of gas has been about the same for both gases.

The symptomatology is the same.

GROUP I. *Dogs Which Die Acutely.*

Deaths occur as early as 2 and 3 hours after exposure to ethyl-dichlor-arsine, and are frequent within 12 hours. In general, it may be said that the acute lesions are similar to those found after exposure to methyl-dichlor-arsine but they are apt to be more severe.

The lungs show marked edema and congestion, without localization in any particular lobes. The color of the lungs is bright red, often with sharply demarcated patches of emphysematous alveoli on the surface (Fig. 1). On section, there is found not infrequently a striking, deep red coloration following the outlines of the bronchial tree (Figs. 8 and 9). The lung tissue for 3 to 5 mm. surrounding the bronchi and vessels is dark red and may stand up slightly above the neighboring alveoli. Under the microscope this is seen to be due to the presence of edema in the alveoli surrounding the bronchi, and to hemorrhages into the alveoli; rarely, they may be present in the sheaths of the blood vessels accompanying the bronchi. This condition has been found in dogs exposed to the other two arsine compounds, but less frequently; it seems to be an expression of the extreme severity of the action of the gas, and occurs in animals which die 12 to 20 hours after exposure (Fig. 10).

In the trachea a false membrane is found quite similar to that described above (Fig. 2). A well-formed but thin membrane has been found in dogs dying as early as 2 hours after exposure; in other cases of very early death, the trachea shows an intense congestion and slight edema without a membrane.

The eye and skin changes also are similar to those described above, and play a minor rôle.

The abdominal organs are often moderately congested, but do not present severe lesions. In the kidney, no necrosis of the tubular epithelium has been found, but the cells of both convoluted and collecting tubules often show swollen and somewhat ragged protoplasm; the nuclei stain well but are occasionally slightly shrunken. Similar minor changes may be found in the liver parenchyma, and minute hemorrhages occur in the adrenals.

GROUP II. *Dogs Which Die from Pneumonia.*

The onset of pneumonia after ethyl-dichlor-arsine has averaged a day or two earlier in our animals than after the methyl compound. It has killed most of the dogs before the end of the second day, but a few have survived 5 to 7 days. The character of the pneumonia is varied and has nothing to distinguish it from that of any other gas.

GROUP III. *Dogs Surviving Long Periods.*

Here again, some dogs have been found which died with pneumonia of an acute type three weeks or more after exposure, and the etiological relationship of the gas is not established. Dogs which have recovered and have been killed for autopsy show no chronic lesions, either gross or microscopic, in the lung parenchyma or in the bronchi.

III. PHENYL-DICHLOR-ARSINE

In discussing this compound there is little to add to the description found under methyl-dichlor-arsine. The same three groups are found, having about the same time factors. The severity of the acute lesions caused by the ethyl compound is not equalled by the phenyl compound as regards edema and peribronchial hemorrhages, but the impression has been obtained that the tracheal membranes formed after exposure to this gas are the thickest and heaviest found after any of the arsines.

A number of dogs have been autopsied after exposure to the gas diphenyl-chlor-arsine. Most of these survived exposure and were killed for autopsy and showed no lesions. Those few dogs which died showed the lesions already described, but did not reach the same degree of severity, and the deaths were not as acute.

A number of dogs were gassed with a combination of diphenyl-chlor- and phenyl-dichlor-arsine, and these were practically indistinguishable from those gassed with phenyl-dichlor-arsine alone. The problem here involved is one of relative toxicity, and the pathological lesions apparently correspond in severity to the amount of phenyl-dichlor-arsine inhaled.

DISCUSSION

It will be seen from the foregoing descriptions that these arsine compounds produce pulmonary lesions analogous to other pulmonary irritants, and have nothing in common with arsine or the compounds of arsenic which cause extensive necrosis of the kidney epithelium. A large number of arsenic compounds were examined with regard to their toxicity and pathological effects by Pearce and Brown, and their results are reported in the J. Exp. Med., 1915, *22*, 517. The effects of these compounds were chiefly on the kidneys; some were particularly destructive to the epithelium of the blood vessels and gave rise to extensive hemorrhages into the necrotic epithelium, producing brilliant red streaks on the yellow kidneys. There was also a marked destructive action on the cells of the adrenals. Pearce & Brown make no mention of any lesions of the lungs. With the arsenic compounds at present under discussion, the method of administration was of course totally different; if arsenic in these forms is active on the kidney epithelium, it is evidently not absorbed through the lungs in sufficient quantities to produce lesions; (in these dogs arsenic is readily demonstrable in the urine).

It seems likely that chlorine rather than arsenic is the important destructive element of these compounds, since their action has so much in common with other chlorinated gases.

SUMMARY

Methyl-, ethyl-, and phenyl-dichlor-arsine are gases belonging to the group of pulmonary irritants. They have edema-producing properties, such as chlorine or phosgene, combined with the epithelium-destroying properties of mustard. The edema produced is not

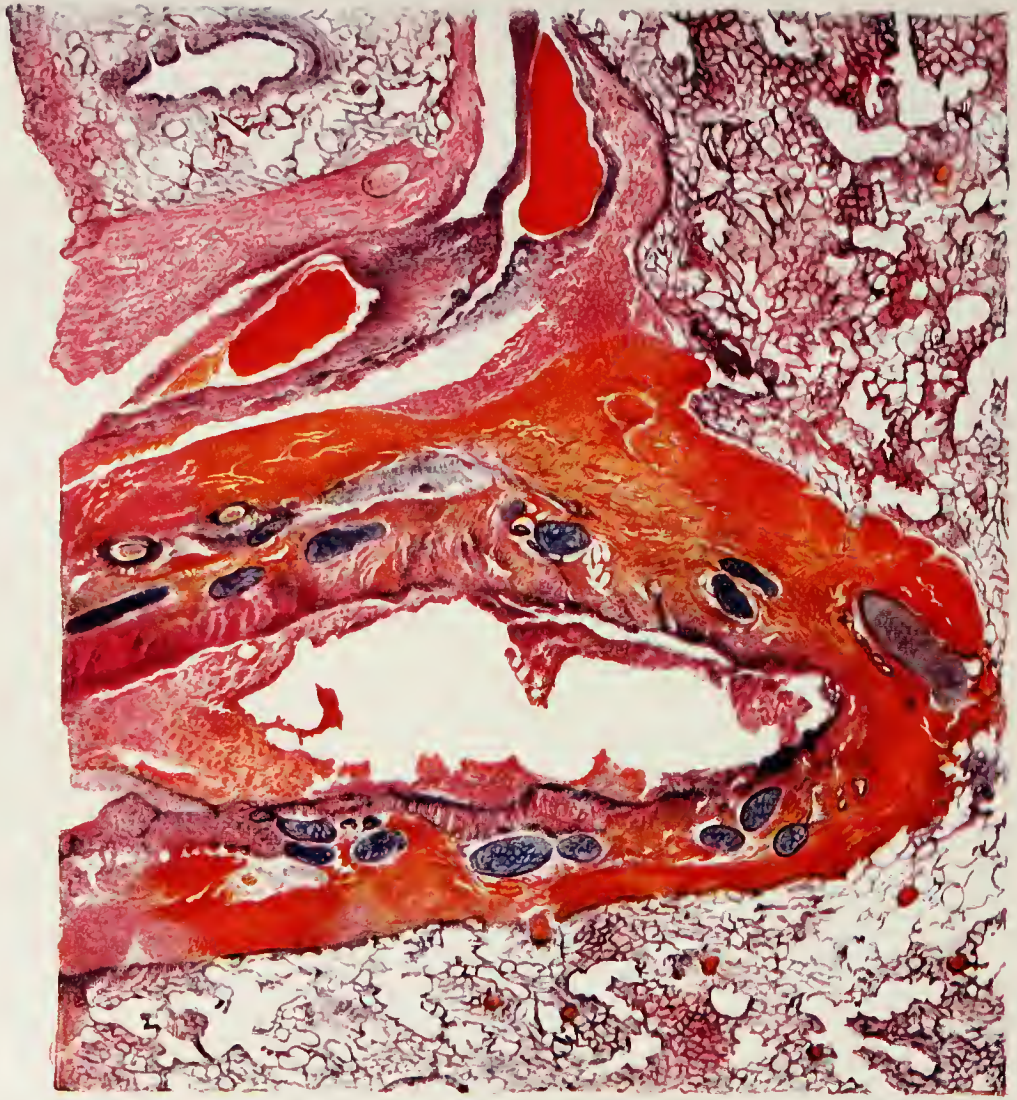
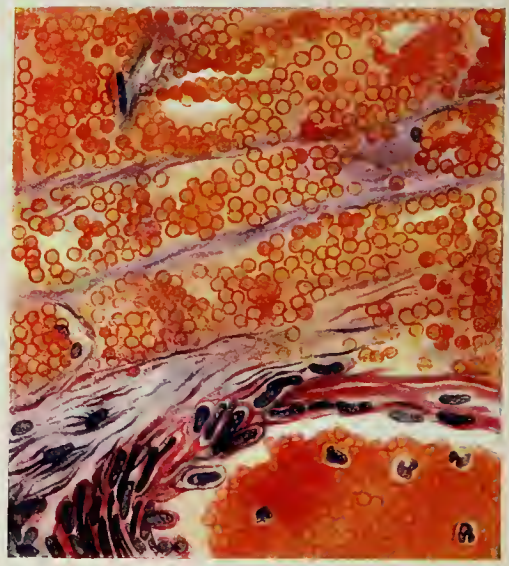


FIG. 10: HEMORRHAGE INTO PERIBRONCHIAL SHEATH WITHOUT EXTENSION TO ALVEOLAR TISSUE; ALSO SOME PERIVASCULAR EDEMA.



ENLARGEMENT OF PORTION OF FIELD TO SHOW RED CELLS. DEATH 20 HOURS AFTER EXPOSURE TO PHENYL-DICHLOR-ARSINE.

PLATE XXXIX

as severe as in phosgene, and the destruction of the bronchial epithelium does not extend as far down into the small divisions of the bronchial tree as in mustard poisoning. The skin-irritant properties cannot be well judged from exposure to vapor in a chamber, but it may be said that the vapor does not attack the skin of dogs under these conditions as severely as mustard, but does much greater damage than chlorine or phosgene. While the acute and temporary discomfort and disablement of the eye are greater with these arsines, there are rarely any permanent effects such as are commonly found after mustard.

PRELIMINARY STUDIES IN INTRATRACHEAL THERAPY

BY

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PRELIMINARY STUDIES IN INTRATRACHEAL THERAPY

INTRODUCTION

It is well known that the circulation in the pneumonic lung is impaired. This condition is not due to the presence of exudate in the alveolus, but rather to the fibrin content of the exudate, as was shown by Kline and Winternitz (J. Exp. Med., 1915, *21*, 311). The conclusion was based upon a series of experiments in which the alveoli were over-distended by means of the insufflation of a gelatin solution. Indeed, it seemed that the slight distention thus brought about actually benefited the circulation. Futhermore, the same impairment of circulation was found to be present when the pneumonic exudate was composed largely of serum and fibrin such as is induced by the insufflation of cultures in animals rendered aplastic by the administration of benzol. On the other hand, in a hirudinized animal, where fibrin formation is inhibited and in which the exudate is rich in leucocytes and red cells, no interference in the circulation followed.

These experiments indicated the inadequacy of a general intravascular therapy in pneumonic conditions and suggested the possibility of the direct application of an intratracheal therapy, analogous to the intrathecal therapy as applied in meningeal conditions.

Preliminary experiments were, therefore, conducted several years ago in which it was shown that the method of intratracheal insufflation, first suggested by Volhard and reintroduced through the extensive experimentation of Lamar and Meltzer, would permit the introduction of relatively large quantities of material directly into the lung. The material so introduced was at least partially absorbed and no serious consequences followed. These experiments were not concluded at the time because of the most promising reports on the type determination of the pneumoccus and the possibilities of a specific serum therapy.

Early in the study of the pathology of the respiratory irritant group of poisonous gases used in modern warfare, the theory was advanced that by an impairment of the protective mechanism of the upper respiratory tract, bacteria were permitted to reach the bronchioles and lung tissue, and so complicate the condition. Further work has substantiated this idea. For example, it has been shown that with chlorine the epithelium of the respiratory tract is killed, and bacteria from the mouth, or even those from without, are able to pass this impaired defensive mechanism; they enter the respiratory tract, and play an important rôle in the development of the pneumonia in animals which survive the most acute stages following exposure to the gas.

The problem of intratracheal or intrabronchial therapy naturally again suggested itself. As a preliminary to the development of such a therapy, it was essential first to determine certain fundamental principles, which are presented below under the captions: 1. Pulmonary irrigation. 2. The efficiency of pulmonary irrigation. 3. Absorption from the lung.

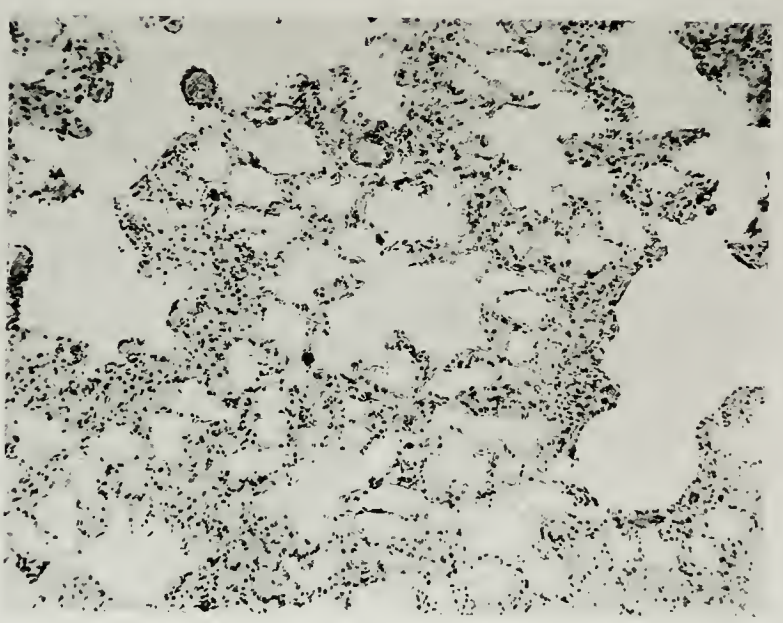

FIG. 2. PN-37. VARIATION IN THE SIZE OF ALVEOLI.

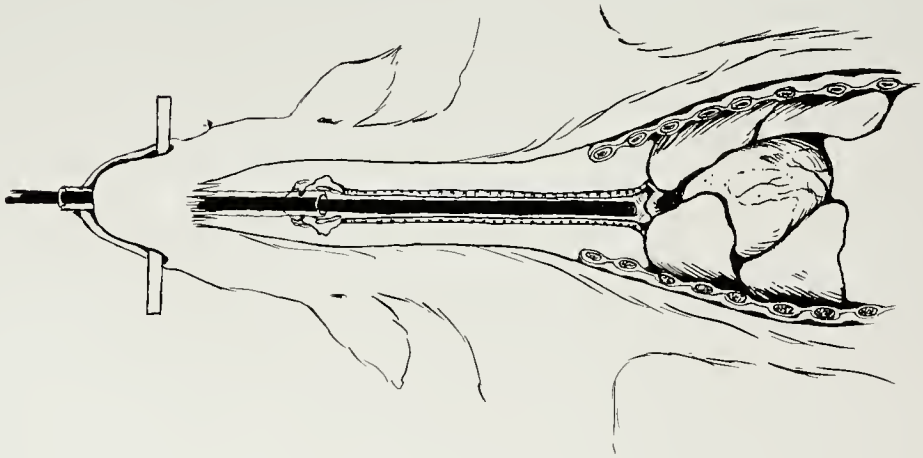

FIG. 1. SHOWING LOCATION OF CANNULA AND GLASS PROTECTING TUBE AS EMPLOYED IN PULMONARY IRRIGATION.

PULMONARY IRRIGATION

It is generally assumed that the lung is very susceptible to the introduction of foreign material. The experiments herein reported were designed to test the validity of such an assumption.

MATERIAL AND METHODS

All the experimental work has been done upon normal dogs, and the material has been brought into the lungs by the ordinary method in intratracheal insufflation. The technic is very simple, and involves no complicated apparatus. A rubber tube of about 8 mm. in diameter and with a heavy wall, which provides the desired rigidity, is passed into a glass tube with a lumen slightly larger than the diameter of the rubber cannula. It is necessary to have the glass tubing of heavy wall to avoid the danger of breakage, and it can be most conveniently manipulated if it is about 20 to 24 cm. in length. After sterilization the glass tube is introduced through the mouth of the animal until the opening is opposite or within the opening of the trachea. During this manipulation the rubber cannula is withdrawn about 2 cm. from the end of the glass tube so that it does not come into contact with the saliva and thus become contaminated. Very gentle pressure exerted upon the rubber tubing that projects from the proximal end of the glass protecting tube is sufficient to force the rubber cannula down through the trachea (Fig. 1). The glass tube thus serves two purposes: it avoids the necessity of directing the cannula into the trachea with the hand, which obscures the vision, and it also permits the passage of the cannula into the trachea without danger of contamination. This same technic can be used equally well if it is desired to pass the cannula into the stomach; and, in fact, unless the glass tube is employed to aid in directing the somewhat flexible cannula, it is not easy to be sure that it is not entering the esophagus when a tracheal introduction is desired. However, that the cannula is in the trachea can be readily determined; for after it has been passed in for a certain distance, that is, as far as the bifurcation of the trachea, its path becomes obstructed. This is not the case when it is entering the stomach. Such manipulation can be done much more readily if the animal is throughly anesthetized.

For the introduction of fluid two methods have been employed, the method of choice depending largely upon the amount of fluid to be introduced. With small amounts, up to 50 cc., satisfactory results have been secured by simply connecting the pipette containing the fluid with the projecting end of the cannula and forcing the fluid in by means of a compression bulb attached to the other end of the pipette. With such small amounts, where it is essential that the material be introduced quantitatively, this method has invariably been employed; for if air is forced through the cannula after the introduction of the fluid, there is no danger of loss. With larger amounts, where a slight loss does not cause an appreciable error or where the material is to be introduced for a long time, the gravity method has been used. In such a case, the cannula is connected by rubber or glass tubing with an elevated reservoir, from which the flow of fluid is regulated by a pinch-cock.

EXPERIMENTS

Employing such technic, a preliminary set of experiments was performed to control quantitatively the tolerance of the lung for fluid. Physiological salt solution was used in quantities ranging from 5 cc. up to 40 cc., regardless of the weight of the animal.

After the insufflation of such small amounts, the animals were allowed to recover from the anæsthetic, attention being directed to any objective symptoms that might be manifest. In no case, could anything of significance be noted, aside from an occasional cough. The majority of the animals were killed within an hour of recovery from the ether. The lungs showed no gross lesions, although a small amount of fluid could be detected in some of the lobes. Of this preliminary series no histological studies were made. It thus appeared that fluid, in small quantities at least, could be introduced into the lung without causing any disturbance in the well-being of the dog or producing gross lesions in the lungs.

With this finding as a basis, a futher serics of experiments was carried out with the object of determining how much fluid could be introduced with safety. To this end, salt solution was insufflated in definitc amounts per kilogram of body weight, starting with 5 cc. per kilogram. Such an amount was tolerated, and the quantity was increased to 20 cc. per kilogram. At this point it became evident that 20 cc. per kilogram approached the limit that could be introduced, not because of any evident harmful effect upon the animal, but simply for the reason that the capacity of the lungs had been reached. Thirty cc. per kilogram was attempted, but before this amount could be completely introduced, there was a flow of fluid back out of the trachea and mouth. In fact, in not every case could 20 cc. of solution per kilogram be introduced without some of the salt solution appearing in the mouth. It should be noted that 20 cc. of solution per kilogram in the dogs with which we were working amounted to between 200 and 450 cc. in total volume.

The protocol given herewith is that for dog Pn-37, the animal mentioned above as having rcceivcd an insufflation of 30 cc. per kilogram of body weight. It is typical of the animals of this series.

Pn-37. 4/9/18. Intratracheal insufflation of physiological salt solution, 30 cc. per kilo. Volume 393 cc., 4:25 P. M. There was an excess of fluid, and after about 275 cc. had been introduced, the excess was expelled. The dog was removed from table immediately and allowed to recover from the anesthesia. During this time some of the fluid escaped from the mouth. There was no manifest distress aside from an occasional cough. 4/10/18. The dog appeared perfectly normal. It was killcd with chloroform. Some fluid not yet absorbed remained in the lung. The surface of the lower right lobe was somewhat mottled and brownish red. The other lobes appeared normal. On section, the lungs showed nothing abnormal. They were pinkish gray in color.

Microscopically: Slight hemorrhage, with an occasional, polymorphonuclear leucocyte, is found in the bronchi. There has been slight mechanical disturbance of the alveoli as evidenced by their variation in size. There is no evidence of fluid or extensive damage. The presence of polymorphonuclear cells within the alveolar walls and a few in the lumen of the alveolus shows that there has been a slight but definite inflammatory reaction (Figs. 2 to 6).

From this series of animals we were able to conclude that salt solution could be introduced in quantities up to thc capacity of the lungs without causing any immediate reaction on the part of thc body as a whole or on the part of the lungs which could be considered sufficiently severe to warrant discontinuance of the work.

Although no immediate severc reaction was secured, the possibility still remained that after the lapse of a longer time, such treatment would produce more serious results. Further, it became of interest to determine how long fluid would remain in the lungs before absorption was complete.

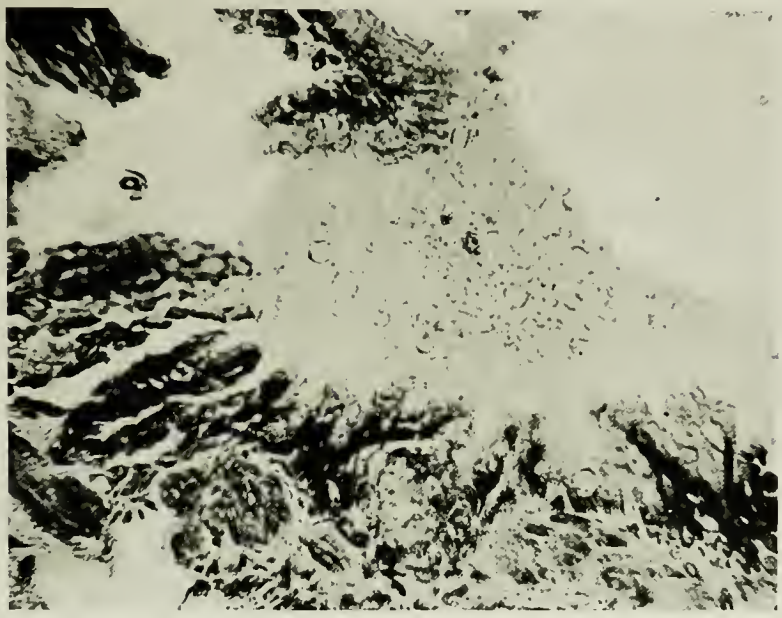

FIG. 3. PN-37. EXUDATE IN BRONCHI.

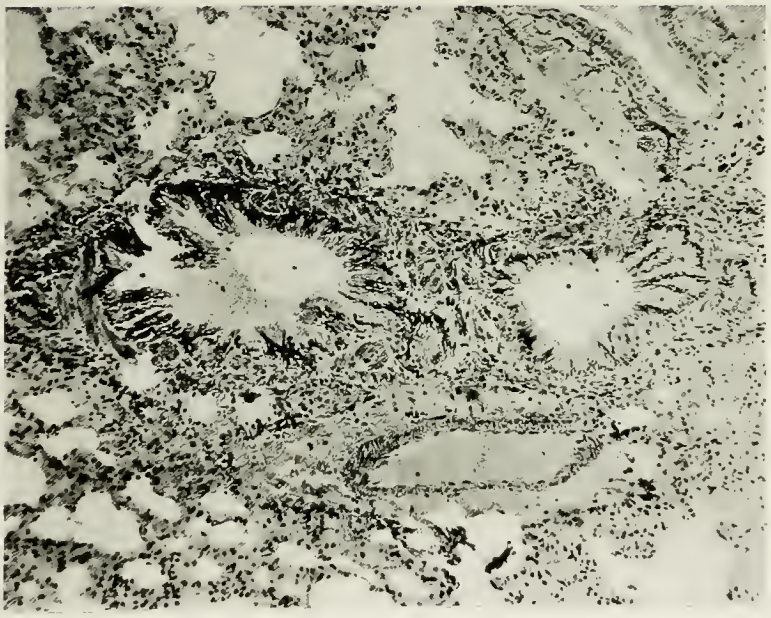

FIG. 4. PN-37. EXUDATE IN BRONCHUS.

A series of dogs, Pn-50 to Pn-55, were each given 20 cc. of salt solution per kilogram of body weight. After varying intervals they were killed, and the lungs were examined. As before, no disturbance was noted in the general condition of the animals immediately after the insufflation or during the period of observation. The protocols for some of these dogs follow.

Pn-50, received 220 cc. salt solution and was killed within 5 minutes of the completion of the insufflation. At autopsy, the lungs, aside from a small portion of the margin of the upper lobes, were found to be completely filled and distended with fluid. In fact, it is difficult to fill the lungs to such an extent that the upper lobes will not be air-containing in some portions. The lungs were normal in appearance except for their distention.

Microscopically: Congestion of the blood vessels and an occasional desquamated epithelial cell and polymorphonuclear leucocyte in the alveoli are the only changes encountered. (Fig. 6).

Pn-52, received 180 cc. of salt solution and was killed after 15 minutes. There were no gross lesions. The lungs appeared as in Pn-50. The dog showed no distress after recovery from the ether.

Microscopically: The picture in the lung was identical with that of Pn-50 aside from the fact that there was evidence of some slight mechanical change in the alveoli and the presence of a few red blood cells in the bronchi.

Pn-51 received 200 cc. of salt solution. It recovered from ether satisfactorily and appeared perfectly well. When killed, after 18 hours, much of the fluid had been absorbed, although there was a considerable amount in the lower lobes. Microscopically, the picture was practically identical with that presented by Pn-52.

Pn-53 and Pn-54. These dogs received 220 and 210 cc. respectively. Both were killed after 4 days. During the interval, they appeared to be perfectly well. At autopsy, the lungs were found to be practically normal with but little fluid remaining. The only gross change was the presence of a few pin-point hemorrhagic areas scattered over the surface of the lower lobes.

Microscopically: Some of the bronchi contained a little mucus with a few red blood cells and an occasional polymorphonuclear leucocyte. The picture suggested that there had been some desquamation of the bronchial epithelium. There was very little inflammatory reaction (Figs. 7 and 8).

Pn-55 received 205 cc. of salt solution. The dog remained apparently normal for ten days, at which time it was killed for examination. The lungs appeared normal, presenting no gross lesions. There was no fluid remaining in any of the lobes. It may be noted that this animal had previously received 40 cc. of salt solution on 2/18/18 with no evidences of distress. Microscopically, the lung tissue appeared normal.

From these experiments, and others which have been performed with slight variations as to time intervals, it is safe to conclude that the lungs can be filled to capacity and that during the period of absorption no marked disturbance occurs. Also, that absorption takes place rather rapidly, since after four days almost the entire volume, amounting to some 200 cc., has been absorbed.

In view of the fact that the lungs can be completely filled with salt solution without harm, and, further, that where amounts larger than 20 cc. per kilogram are employed, there is an overflow of fluid from the lungs, it seems possible that even larger quantities of solution can be tolerated, as in perfusion. The following experiments demonstrate that such is the case.

In this work ten dogs have been used. The perfusion fluid has been administered either continuously or intermittently and in quantities of 2500 or 3000 cc. The period of perfusion has been, as a rule, 30 to 35 minutes, during which time the entire 3000 cc. will pass through the lung. In a single case (Pn-102), the dog has been subjected to perfusion for two hours with a volume of 3000 cc. In experiments where such large volumes are administered, the gravity method has been used.

In intermittent perfusion, the lungs are flooded with salt solution, and then the flow from the reservoir is cut off for a few minutes, during which time the lungs drain somewhat. After the solution ceases to flow out of the trachea and mouth, the lungs are again flooded. With the continuous method of perfusion, the force of the flow from the reservoir is cut down, and a small stream is allowed to enter the lungs throughout the experiment. It would seem that the intermittent method is better tolerated by the animal, since with continuous perfusion, artificial respiration may occasionally be necessary. With the intermittent method, there seems to be no serious interference with the respiration; the dog recovers from the anæsthetic satisfactorily, although slowly, and appears well. During such treatment, it is rarely necessary to administer ether after the lungs are filled with solution and the flow is established.

In most of the experiments in which perfusion has been employed, points other than the tolerance of the animal to the mechanical effects of the perfusion have been involved. Therefore only two protocols are given.

Pn-56. 6/13/18. After perfusion of 3000 cc. of salt solution within 30 minutes, the dog was killed and autopsied. The lungs were filled to capacity. There were no gross lesions. During the perfusion the respiration continued evenly, although shallow. A continual bubbling of air and fluid in the throat took place with each breath. At first the bubbles were frothy; later the froth disappeared and the material appeared to be pure salt solution. Microscopically, there was definite desquamation of the cells of the alveolar walls. There were some red blood cells and scattered polymorphonuclear leucocytes in the alveoli as well as a few macrophages with ingested red cells. The bronchi contained a slight excess of mucus, together with some desquamated cells and a few erythrocytes.

Pn-58. 6/15/18. After perfusion of 3000 cc. of salt solution within 35 minutes, the dog recovered satisfactorily and appeared drowsy during the remainder of the afternoon. (Perfusion completed at 3:05 P. M.) On the next day and the succeeding day, the dog appeared normal and was killed for examination on 6/17/18. No gross lesions were found aside from a number of very small areas of hemorrhage, located largely on the lower lobes. There was much fluid in the lower lobes. The upper lobes were free. The microscopic picture was identical with that of Pn-56 (Figs. 9 and 10).

These results show that fluid in large amounts can be perfused without difficulty through the lung during a considerable space of time. In fact, no evidence presented by the work thus far would indicate that much larger quantities of solution can not be introduced, or that the perfusion can not be continued for an indefinite period.

The question naturally arose as to whether the salt solution was actually passing through the lung, or whether it was simply flowing out of the cannula into the larger bronchi and thence back out of the trachea without entering the lung proper. A single experiment sufficed to demonstrate that the fluid was actually entering the lung.

Pn-57. Perfusion of 2500 cc. of salt solution 6/14/18. Without removing the cannula or stopping the flow from the reservoir, a solution of India ink was added to the last fluid to enter the lung. The lungs were immediately exposed before the fluid had an oppor-

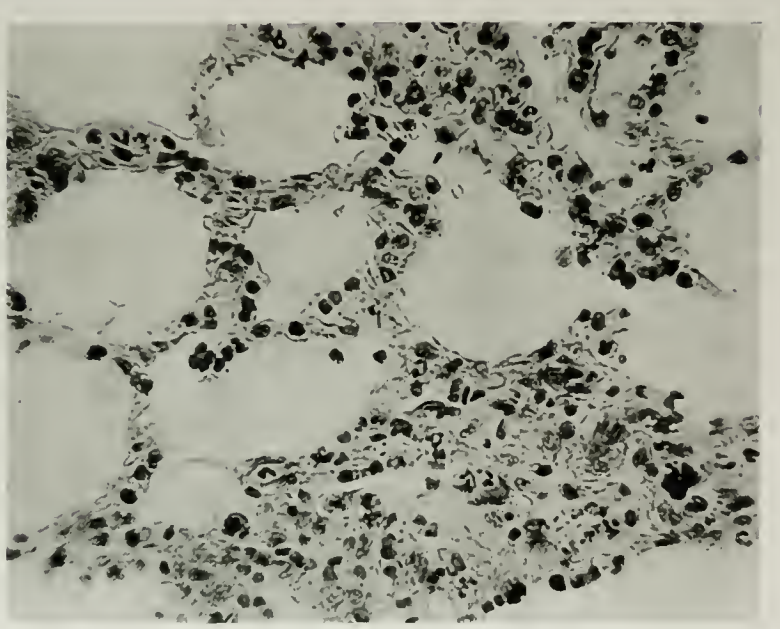

FIG. 5. PN–37. CONGESTION IN ALVEOLAR WALLS.

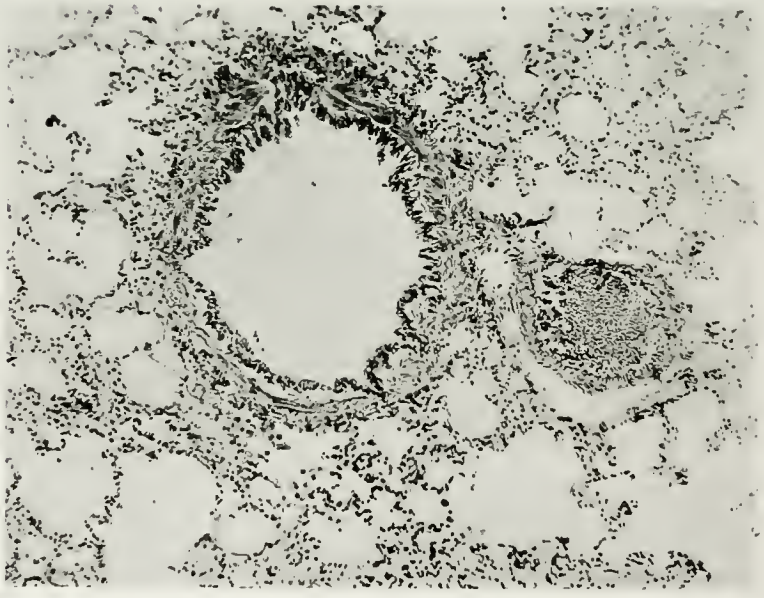

FIG. 6. PN–50. BRONCHUS SHOWING EXTENT OF DAMAGE.

tunity to drain from them. It was found that the India ink had penetrated and stained the lower lobes throughout, and was scattered in patches throughout the upper lobes. None of the lobes were free from this staining.

SUMMARY

From these experiments it is evident that the lung is not as sensitive to the introduction of fluid as has been assumed. Large quantities of salt solution can be introduced without serious disturbance to the general condition of the animal, and without causing gross destruction to the lung tissue. The histological lesions found are insignificant.

Absorption of considerable quantities of fluid can be brought about within a few days (3 to 4), and within 10 days, the lung has returned to normal.

The lungs can be subjected to perfusion with an interchange of fluid throughout all lobes.

THE EFFICIENCY OF PULMONARY IRRIGATION

As shown above large quantities of salt solution can be passed through the lung with safety. In the course of such perfusions, it became apparent that the character of the fluid flowing from the mouth during the treatment changed markedly. The first portions of the effluent contained much mucus, and were thick and stringy. As the perfusion progressed the fluid became limpid and water-clear. It appeared that the saline in bubbling through the throat washed out the secretions.

During some experiments, designed primarily for other purposes, a test was made of the efficiency of this process in removing the bacteria of the mouth. At intervals as the perfusion progressed, samples of the effluent from the mouth were collected and bacterial counts were made. The results of such counts with two dogs, Pn-57 and Pn-58, follow.

Pn-57. 6/14/18. Total perfusion volume 2500 cc.

Samples of the effluent were taken after 250, 1000, and 2000 cc. of solution had passed through the lung. These samples were plated on blood agar in 0.05 cc. amounts.

Sample after perfusion of	*Bacterial counts*
250 cc.	Infinity (very many green pigmented colonies)
1000 cc.	25 (no green pigmented colonies)
2000 cc.	45 (no green pigmented colonies)

Pn-58. 6/15/18. Total perfusion volume 3000 cc.

Samples of the effluent were taken after 500, 2000, and 3000 cc. of the solution had passed through the lung.

These samples were plated on blood agar in 0.05 cc. amounts.

Sample after perfusion of	*Bacterial counts*
500 cc.	Almost infinity (few green pigmented colonies)
2000 cc.	4 (no green pigmented colonies)
3000 cc.	11 (no green pigmented colonies)

While these tests are primarily quantitative, and are qualitative only with respect to the recognition taken of colonies which developed a green pigmentation upon blood agar; yet they show that the mechanical effect produced by treatment serves to free the mouth of a large proportion of its normal flora.

Such procedure does not, however, give any information as to the efficiency of the perfusion treatment in the removal of material from the lungs. A number of experiments designed to test this point have been performed, employing a number of substances, such as India ink, protargol, starch paste, and bacteria, as indicators.

Pn-59. 6/15/18. Intratracheal insufflation of 20 cc. of a heavy suspension of India ink was followed by a saline perfusion during a period of 20 minutes of 2500 cc. The animal was killed and autopsied at the completion of the perfusion. All lobes of the lung contained much fluid, but showed no apparent lesions. Only the lower right lobe was stained with ink. Throughout its upper two-thirds, the stained areas were scattered, some portions being unstained, but in the lower third the ink was everywhere present, in greatest concentration along the lower margin. During the perfusion the effluent, at first deeply stained with ink, became increasingly clear, and at the end of the perfusion, was but slightly tinted.

It is evident that although much of the ink had been washed out, some still remained in the lung. It was thought that protargol might be a better indicator than ink, as it appeared that the latter adhered very firmly to the tissue.

Pn-60. 6/15/18. Insufflation of 15 cc. of 20 per cent. protargol.

Perfusion with 3025 cc. of saline solution within 35 minutes.

The first portions of the effluent were stained a very deep brown. As the perfusion continued, the color became less in intensity, although even after washing with 3025 cc. of saline, the effluent was lightly tinged with the test solution. The dog was killed and autopsied immediately. All lobes were distended with fluid. Relatively little protargol remained, and that which had not been washed out was distributed in patches throughout the lower right lobe.

It may be concluded that the perfusion had washed out a large porportion of the material introduced. The lung showed a marked contrast with that of another dog which served as a control and which had received the protargol without the subsequent perfusion. In this control animal, the entire lower right lobe was deeply stained, as were also portions of the upper lobes on the right side and the left lower lobe.

Protargol, like India ink, is not an entirely satisfactory indicator, since it seems actually to stain the tissue in such a way that washing will not entirely remove it. Thus, as a further test of the method of perfusion, attempts were made to wash out starch paste.

Pn-61. 6/16/18. Insufflation of 20 cc. of a dilute solution of starch paste was followed by a continuous perfusion during 25 minutes of 3000 cc. of salt solution. Throughout the experiment the effluent continued to give a positive iodin-starch reaction. At the end of the perfusion, the dog was killed and autopsied. The lungs were removed, and after the different lobes had been cut with several incisions at different levels, they were tested for the iodin reaction. A positive reaction was secured with the lower right lobe. The starch was uneven in its distribution. All of the larger bronchi and the majority of the smaller ones were free of starch.

Pn-62. 6/16/18. The above experiment was controlled by insufflating an animal with the same amount of starch paste and testing the lungs in the same manner without perfusion. The lower right lobe was full of starch, as was also a portion of the ad-

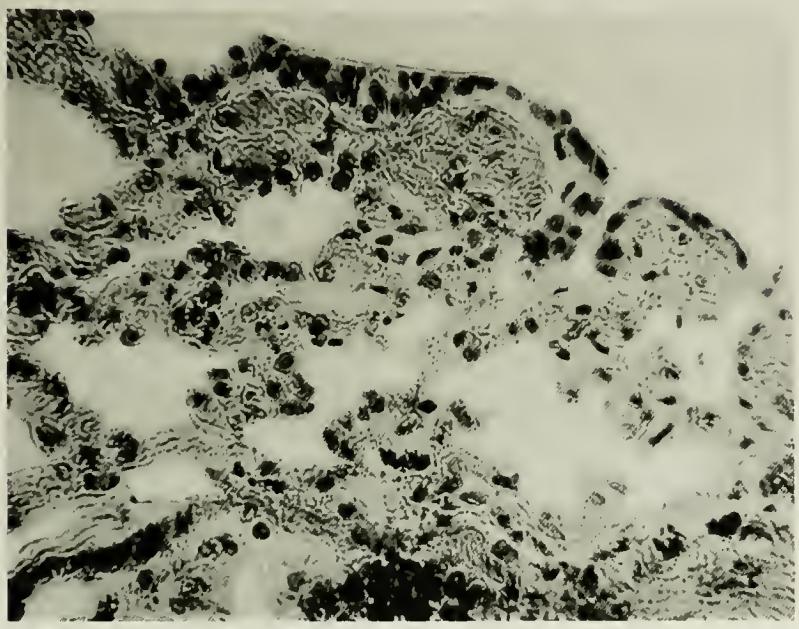

FIG. 7. PN-53. EDGE OF BRONCHUS SHOWING EXTENT OF INFLAMMATORY REACTION.

FIG. 8. PN-53. BRONCHUS SHOWING EXTENT OF DESQUAMATION OF EPITHELIAL CELLS.

jacent upper lobe. All of the bronchi, from the large ones to those microscopic in size, were filled with the paste.

From all these experiments with several indicators, it may be concluded that perfusion is effective to a certain extent in eliminating material injected into the lungs. Although some of the material injected invariably remained, it is evident that much of it passed out with the effluent. However, no quantitative means was employed to measure either that portion which remained or that portion which was removed. The two experiments which follow, while not strictly quantitative, serve to show that perfusion is effective.

Pn-99. Insufflation of 15 cc. of a very heavy 24-hour broth culture of *B. prodigiosus*. The tracheal cannula was removed and sterilized. Saline perfusion of the lung to the amount of 3000 cc. lasting 45 minutes, was started about 20 minutes after the introduction of the culture. The perfusion was by the intermittent method. At intervals during the perfusion, samples were taken from the effluent. These were plated in dilutions for the count of *B. prodigiosus*.

Samples after perfusion of	*Count, per cc.*
300 cc.	2,075,000
600 cc.	970,000
1000 cc.	260,000
2000 cc.	90,000
3000 cc.	80,000

Pn-102. Insufflated with the same amount of a similar culture. Cannula sterilized. Continuous perfusion with 3000 cc. lasting over 2 hours. Counts made as before.

Samples after perfusion of	*Count, per cc.*
250 cc.	548,000
500 cc.	406,000
1000 cc.	288,000
2000 cc.	156,000
3000 cc.	56,000

SUMMARY

Perfusion of the lung with large volumes of salt solution is effective in removing such material as India ink, protargol, starch paste, and bacteria. From the nature of the substances employed as indicators, no quantitative data can be derived as to the exact efficiency of removal.

ABSORPTION FROM THE LUNG

It has been shown that salt solution introduced into the lungs of normal dogs by intratracheal insufflation is absorbed with considerable rapidity. In so far as can be determined small quantities, such as 30 to 50 cc., disappear within 48 to 72 hours.

In order to secure more precise data on the facility with which absorption takes

place from the lung, the absorption of phenolsulphonephthalein has been measured. That variation in renal excretion be excluded, the rates of absorption after intratracheal insufflation and after intramuscular and intravenous injections have been determined in the same animals.

The amount of the phenolsulphonephthalein introduced has always been the same, 6 mg., although in the case of the intratracheal insufflations, this quantity was contained in 15 cc. The volume of the intramuscular and intravenous injections was 1 cc. The elimination was measured in dogs anesthetized with ether. Before the injection of the drug, the dogs were given 250 cc. of water by stomach and a catheter was passed into the bladder. After the injection or insufflation of the phenolsulphonephthalein solution, the contents of the bladder were removed and tested every five minutes until excretion of the drug was detected.

In addition to the tests for the time of appearance of the phthalein, the urinary excretion for half-hourly periods was collected separately, the bladder being washed out at the end of every such period, and each specimen was tested for its phthalein content. Such collections were made up to 2 hours after the introduction of the drug. Two typical protocols are here presented.

Pn-87. 6/28/18. 250 cc. water into stomach at 10:39.
6 mg. (in 15 cc.) into lung at 10:42.
The drug appeared in the urine at 10:55 (13 minutes).
Urine excreted collected in half-hourly periods.
Titrations

1st half hour	12.5%
2nd half hour	20.0%
3rd half hour	16.6%
4th half hour	8.0%
Total:	57.1% (2 hours)

7/15/18. 250 cc. water into stomach at 2:37.
6 mg. phthalein injected intramuscularly at 2:39.
The drug appeared in the urine at 2:54 (15 minutes).
Urine excreted collected in half-hourly periods.
Titrations:

1st half hour	5.5%
2nd half hour	26.0%
3rd half hour	17.0%
4th half hour	24.0%
Total:	72.5% (2 hours)

7/16/18. 250 cc. water into stomach at 9:58.
6 mg. phthalein into jugular vein at 10:17.
The drug appeared at 10:22 (5 minutes).
Urine collected at half-hourly periods.

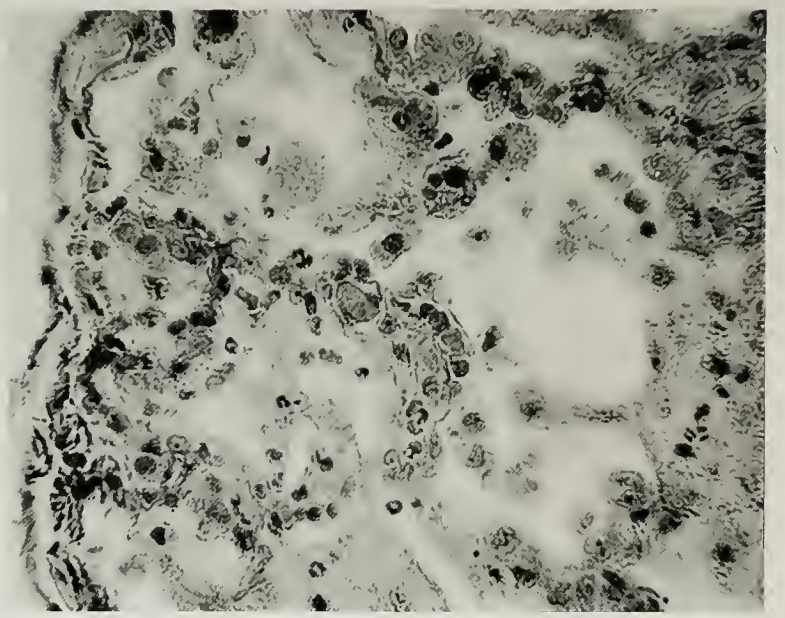

FIG. 9. PN-58. RED CELLS INGESTED BY MACROPHAGES.

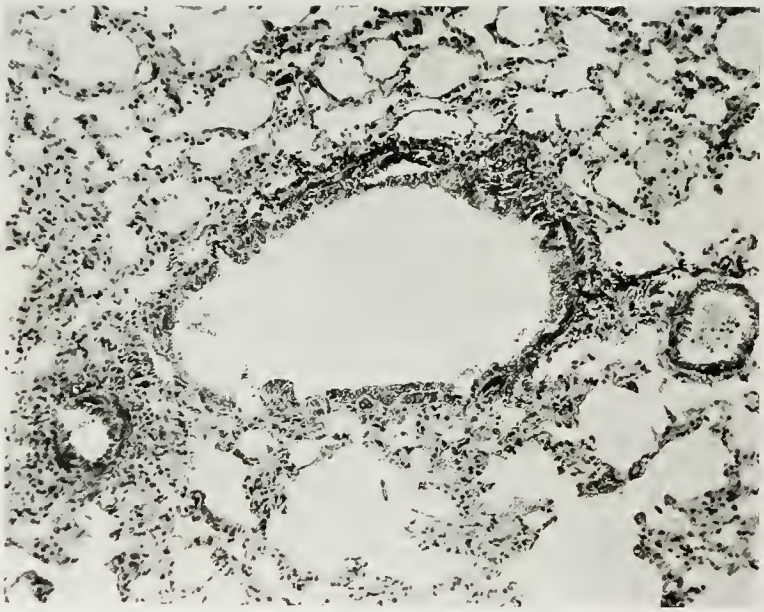

FIG. 10. PN-58. BRONCHUS SHOWING EXTENT OF DAMAGE.

Titrations:

1st half hour	24%
2nd half hour	36.4 %
3rd half hour	10.5 %
4th half hour	7.25%
Total:	78.15% (2 hours)

A tabulation of these results, arranging the values in parallel series shows:

	Intrapulmonary	*Intramuscular*	*Intravenous*
First positive	13 min.	15 min.	5 min.
1st half hour	12.5%	5.5%	24.0%
2nd half hour	20.0%	26.0%	36.4%
3rd half hour	16.6%	17.0%	10.5%
4th half hour	8.0%	24.0%	7.2%
Total:	51.1%	72.5%	78.1%

These figures, secured with an animal which gave a fairly high rate of excretion, show that there is a very close relationship between absorption from the lung and absorption following other methods of administration of the drug. In the protocols which follow, the values for phthalein excretion (or possibly of absorption) are uniformly lower. However, the same relationship between the several methods of introduction exists, excretion after absorption from the lung being comparable with the results secured from the other methods of administration.

Pn-105.

7/11/18. 250 cc. water into stomach at 2.12.

6 mg. phthalein into lung at 2.27.

First appearence of drug in urine at 2.42 (15 min.).

Urine collected in half-hourly portions.

Titrations:

1st half hour	1.25%
2nd half hour	2.75%
3rd half hour	2.50%
4th half hour	0.75%
Total:	7.25% (2 hours)

7/15/18. 250 cc. water into stomach at 2:05.

6 mg. phthalein into muscle at 2:07.

First appearance of drug in urine at 2:52 (45 minutes).

Urine collected in half-hourly portions.

Titrations:

1st half hour	0.0
2nd half hour	trace
3rd half hour	0.5%
4th half hour	1.5%
Total:	2.0% (2 hours)

7/18/18. 250 cc. water into stomach at 2:10.
6 mg. phthalein into circulation at 2:16.
First appearance of drug in urine at 3:03 (47 minutes).
Urine collected in half-hourly portions.
Titrations:

1st half hour	0.0
2nd half hour	3.25%
3rd half hour	1.7%
4th half hour	3.0%
Total:	7.95% (2 hours)

Tabulated in parallel series:

	Intrapulmonary	*Intramuscular*	*Intravenous*
First positive	15 min.	45 min.	47 min.
1st half hour	1.25%	none	none
2nd half hour	2.75%	trace	3.25%
3rd half hour	2.50%	0.5%	1.7 %
4th half hour	0.75%	1.5%	3.0 %
Total:	7.25%	2.0%	7.95%

In a number of other dogs the absorption from the lung has been compared with absorption after intramuscular injection. In every case the results indicate that the absorption from the lung is comparable to that from the muscles.

The only conclusion derived from the experiments cited above is that the normal lung is able to function as an organ of absorption with a degree of efficiency equal to the other tissues tested.

SUMMARY

The lungs can tolerate the introduction of fluid (salt solution), even in large quantities, without consequent serious damage.

Moderate quantities of fluid, that is, up to the capacity of the lungs, can be insufflated without difficulty, and the absorption of this fluid follows very rapidly, leaving no evidence of marked change.

Experiments upon the absorption of phenolsulphonephthalein show that absorption from the lung proceeds as readily as from muscle.

Pulmonary irrigation is possible, and there are no attendant ill effects.

Such irrigation not only removes material from the mouth and trachea, but the fluid actually penetrates the smaller air passages of the lung, with the result that materials employed as indicators are in large part removed by the mechanical effect of the saline irrigation.

These experiments suggest the possibility of an intratracheal therapy, based either upon intratracheal insufflation or upon pulmonary irrigation.

THE SIGNIFICANCE OF HEMORRHAGES IN RESIDUAL PULMONARY LESIONS FROM RESPIRATORY IRRITATING GASES

BY

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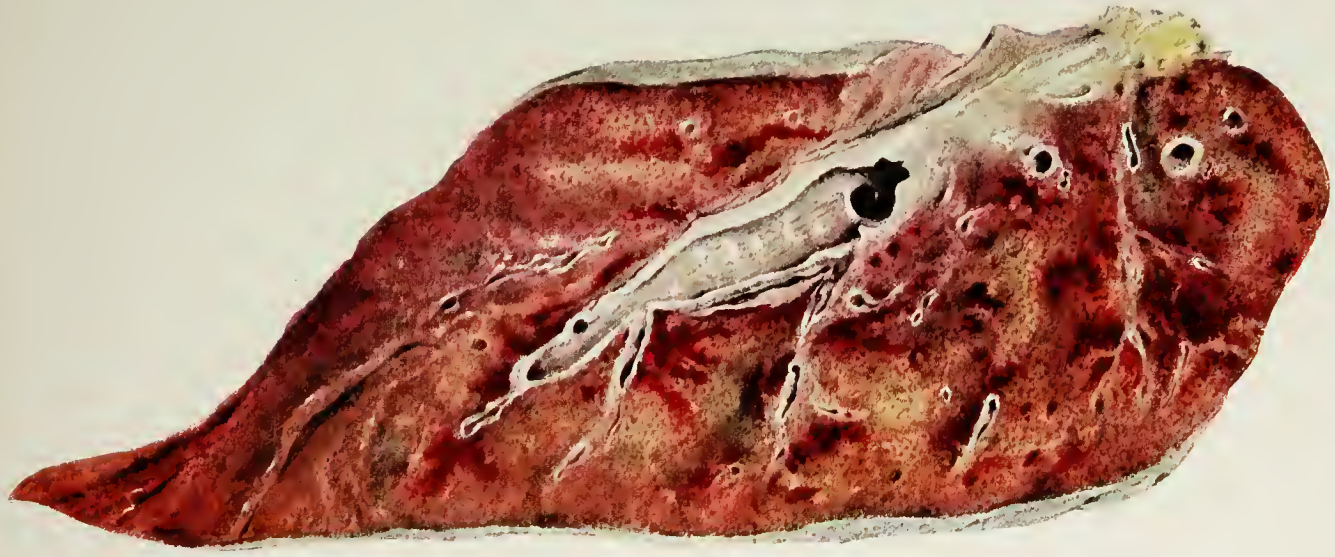

PLATE XL

FIG. 1: HEMORRHAGES IN LUNG OF DOG KILLED 10 DAYS AFTER PHOSGENE GASSING. MICROSCOPICALLY THE SITE OF EACH HEMORRHAGE IS FOUND TO BE A FOCUS OF ORGANIZING BRONCHIOLITIS.

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HEMORRHAGES IN THE VISCERA IN ANIMALS THAT SUCCUMB ACUTELY TO POISONOUS GASES

Reference has been made in previous papers to hemorrhages in the pleura and endocardium of animals dying in the *acute* stage after gassing by chlorine, phosgene, chlorpicrin, and other gases of the respiratory irritant group. In respect to size, location, and distribution, these hemorrhages do not differ essentially from those seen in man in association with some of the severe infections or toxemias. In the lungs, these are often overlooked at autopsy by the casual observer, owing to the extreme congestion and edema present, which dominate the picture. The posterior surface of the lung is the site of predilection, but dark red patches of blood may be seen occasionally in the substance of the organ. Microscopic foci are more often discovered in the body of the lung. The sub-endocardial hemorrhages are very conspicuous and not easily overlooked. They occur most often in the left ventricle, are generally multiple, and distributed lengthwise along the crests of the muscular pillars and ridges. Now and then they are found about the bases of the valve cusps,—mitral, tricuspid, or semilunar.

The hemorrhages in these *acute* deaths are frequently so extensive that they must be the result of rhexis and not simply an inflammatory diapedesis.

It, however, is not our intention to discuss these, as it is obvious that the hemorrhages in this acute period are of secondary importance. They are referred to here only by way of introduction to some observations on hemorrhages in "chronic" or "recovered" gassed animals, that is, animals that have passed successfully the acute edema period. The findings in these chronic animals will be given in some detail, since they appear to us to have an important bearing on the progression of the pulmonary lesions.

HEMORRHAGES IN THE LUNGS OF ANIMALS THAT HAVE SURVIVED EXPOSURE TO POISONOUS GASES

In our first series of autopsies on animals which had died five days to several months after gassing with phosgene and chlorine, hemorrhages in the lungs were recorded in approximately 35 per cent. The cause of death in a majority of these cases was respiratory infection of one type or another, generally broncho-pneumonia, associated with an acute and chronic bronchitis.

In a second series of autopsies on "chronic dogs" that were *killed* ten days to five months after gassing, it was noticed that hemorrhages in the lungs were much more regularly encountered than in the animals that died, about 90 per cent. as compared with 35 per cent. Furthermore, the hemorrhages were larger and more widely distributed. In most cases they were quite fresh, indicating that they had occurred just before death. These dogs had been killed with strychnia; and all died in convulsions, which sometimes lasted over several minutes.

In order to determine to what extent the convulsions were responsible for the hemorrhages, other methods of killing were resorted to.

The dogs were divided into three groups. Those of the first group were killed with potassium cyanide (subcutaneous injection); of the second, with chloroform (forced inhalation); of the third, by a shot through the head from a small calibre pistol.

The dogs killed with chloroform were forced to breathe through an ordinary anesthetizing cone. Most of the animals struggled considerably. Hemorrhages in the lungs were found grossly in 60 per cent. of these dogs and this figure was increased to 65 per cent. by a microscopic study of the lungs.

The cyanide dogs died within a few minutes after the injections. Some showed only a slight rigor; in others there were definite convulsions, but never as marked or prolonged as in the dogs killed with strychnia. At autopsy, the lungs showed hemorrhages in approximately 50 per cent.

The dogs that were shot died with less struggle. Hemorrhages were demonstrable in only 30 per cent., and in some of the positive cases, the lesions were obviously not recent.

From these observations we may conclude:—

(*1*). That hemorrhages occur in a little less than half of the "chronic" gassed dogs which *die* from respiratory infection or other cause.

(*2*). That hemorrhages are present also in animals that are *killed*, but the per cent. showing hemorrhages varies with the method of killing, strychnia giving almost 100 per cent., shooting, 30 per cent.

In brief, it appears that the lung of an animal that has been gassed is a favorable site for hemorrhage, and that hemorrhages into such a lung are easily induced by struggling or convulsions.

It may be mentioned that a few normal control animals were killed by the methods mentioned, and that while strychnia and chloroform produced hemorrhages in some cases, the lesions were never as extensive as in the gassed dogs.

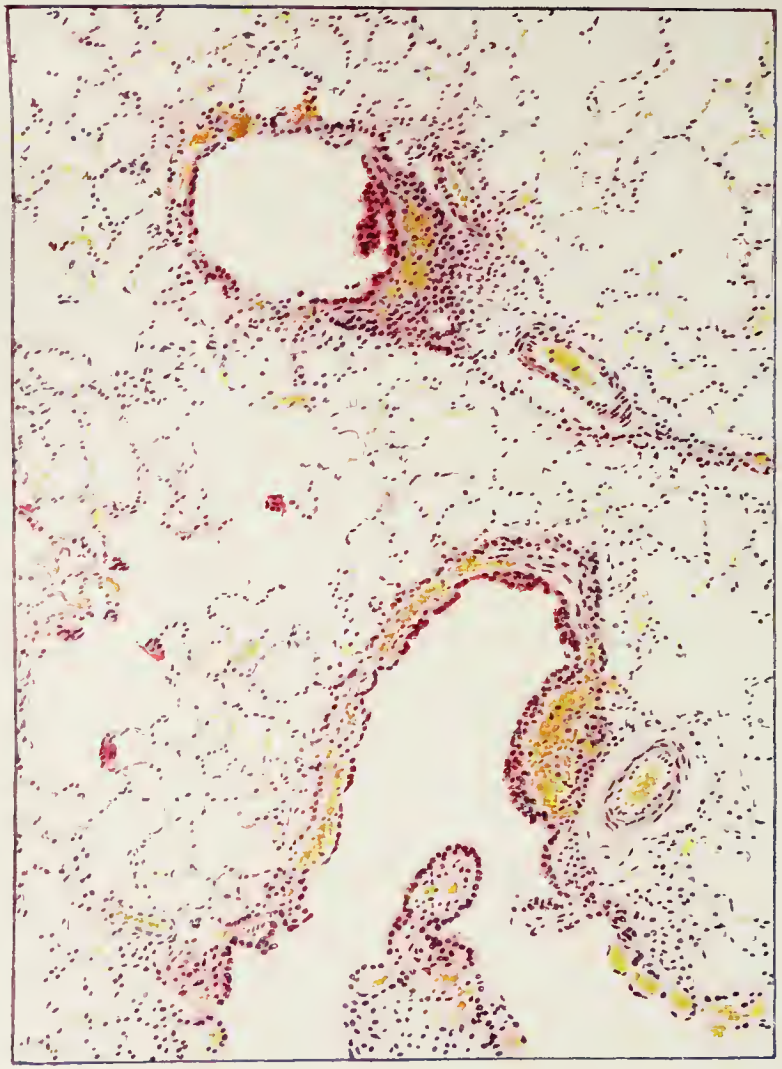
The character of the pulmonary hemorrhages in these gassed dogs and the relation to the chronic inflammatory or reparative lesions so regularly found in the lungs (see Chlorine and Phosgene papers), are points which have interested us particularly. A brief description of the hemorrhages will suffice.

Grossly, the hemorrhages may resemble those seen in the acute stage; that is, they appear as irregular sub-pleural extravasations, of variable size and number, situated generally on the posterior surface. But more often they appear as nodules in the substance of the lung. These nodules, generally irregularly spherical in outline, vary in size from a millimeter to several centimeters in diameter. The larger ones are surrounded by a light zone of non-collapsed lung tissue, evidently the result of pressure of the hemorrhage on a bronchus. The relation of some of the smaller hemorrhages to bronchi is often quite clear.

In dogs killed in the subacute period, five to ten days after gassing, the hemorrhagic foci often coincide with the fine nodules of organizing bronchiolitis, described in previous papers (Fig. 1).

Perhaps the most striking type of hemorrhage is where the blood forms a sort of halo or ring about a good-sized artery. This picture clearly is produced by the rupture of one of the vasa vasorum with the escape of blood into the perivascular sheath.

Similar hemorrhages in the human brain following gassing by phosgene have been described by Mott.



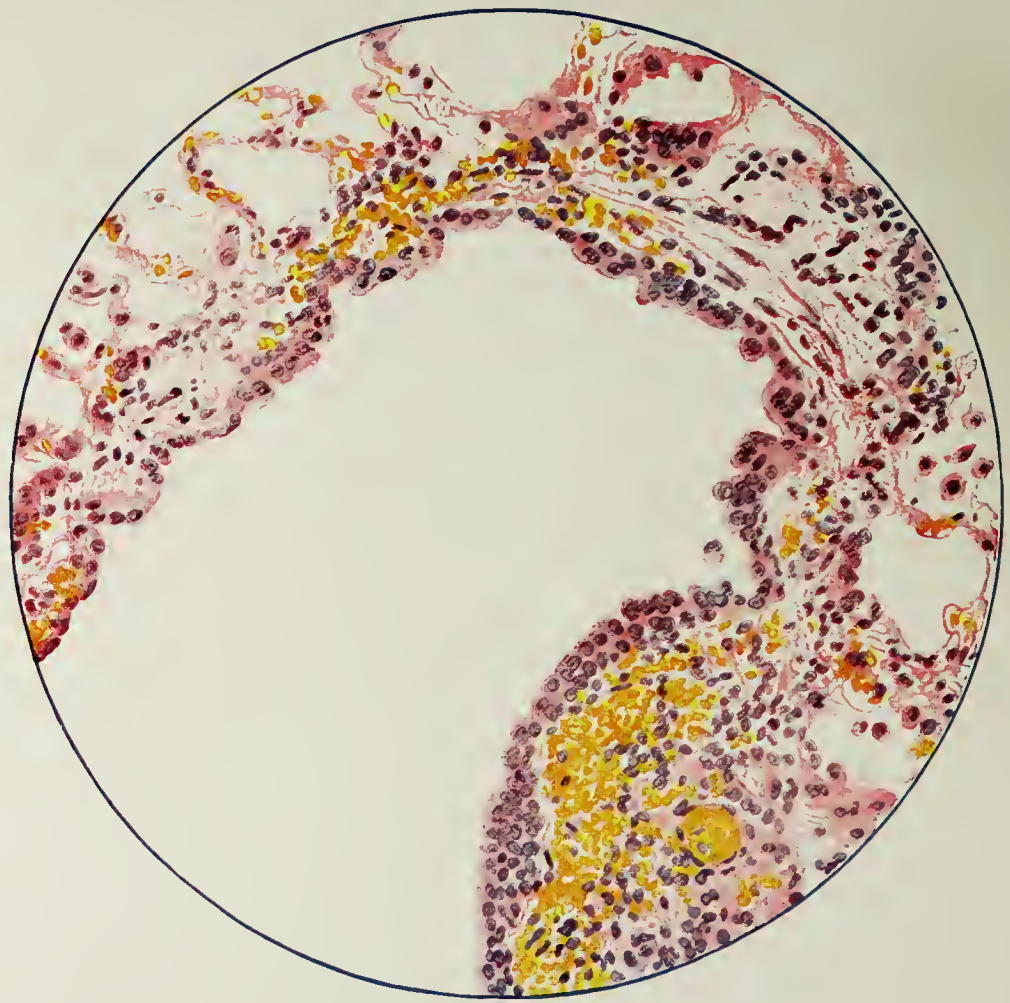


PLATE XLI

FIG. 2: HEMORRHAGES IN WALL OF DAMAGED BRONCHUS 6 DAYS AFTER CHLORPICRIN GASSING. ANIMAL KILLED. NOTE REGENERATION OF BRONCHIAL EPITHELIUM.

FIG. 3: HIGHER MAGNIFICATION OF HEMORRHAGE IN WALL OF BRONCHUS SHOWN IN FIG. 2. REGENERATION OF BRONCHIAL EPITHELIUM IS ALSO SEEN.

Is there any relationship between these hemorrhages and the chronic infection and reparative changes which characterize the gassed lung? In answer to this question, it can be stated on the basis of microscopic examination of a large number of lungs, that in practically every case in which hemorrhages are found, focal lesions of one type or another are also demonstrable. Furthermore, in many cases, but especially in dogs killed in the subacute period (five to ten days after gassing) the hemorrhages are seen to originate directly in these lesions (Fig. 2).

In addition to fresh hemorrhages one sees not infrequently, patches of disintegrating blood cells and scarred areas containing blood pigment. The presence of these would suggest that hemorrhages are not only the *effect* of a scarred damaged lung, but may also be the *cause*. The delicate vessels of the scar are prone to rupture. The resulting hematoma becomes organized with the formation of more scar tissue. In other words, it seems possible that in these chronic lesions of the lungs and in hemorrhages, we may have a vicious circle, with sudden increase in blood pressure (induced by excessive physical effort, struggling, convulsions, or other cause) as the force which keeps the process going.

Hemorrhages as an expression of an acute exacerbation of a chronic lesion are not uncommon occurrences in human pathology. They are most striking perhaps in the contracted kidney of Bright's disease, where a sufficient explanation of their etiology has not been forthcoming. It seems unlikely that they are brought about except in a small minority of cases by reinfection. On the other hand, the experiments of Wiesel and Hess (Wien. klin. Woch. 1913, *26*, 317. Ztschr. f. Exp. Path. u. Ther. 1915, *17*, 74), repeated and simplified in unpublished results obtained several years ago by one of us, are suggestive. It is possible to produce hemorrhagic glomerular and interstitial lesions in the acute uranium kidney by sudden blood-pressure changes brought about with digitalin, strophanthin, adrenalin, etc. Perhaps the high blood pressure associated with the contracted kidney may be able to produce vascular rhexis in the abnormal kidney, rendered more susceptible by a mild parenchymatous change. While there may be some question about this conclusion, the experiments above quoted are sufficient to associate hemorrhage with acute blood-pressure elevation in pathological organs.

CONCLUSIONS

The conclusions to be drawn from the foregoing observations upon hemorrhages in the lungs of chronic gassed animals are: (*1*) The chronic inflammatory and reparative changes in these lungs create a condition favorable to hemorrhage. (*2*) Hemorrhages are induced in such lungs by sudden increase in blood pressure. (*3*) Hemorrhages may lead to further scarring of the lung, which again favors bleeding, thus constituting a vicious circle.

The application of the lesson contained in these findings appears to be clear. A soldier that has recovered from the acute effects of gassing should be regarded as an individual with damaged lungs, and should avoid muscular effort or other practices or conditions which might lead to increased blood pressure. Otherwise pulmonary hemorrhages are likely to occur. While these are probably never extensive enough to cause death, they will undoubtedly accentuate the chronic scarring of the lung already present, which will, in turn, lead to further disablement of this organ.

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